THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 58 DECEMBER, 1947 No. 6

THE DIFFERENTIATION OF PATENT DUCTUS ARTERIOSUS AND ATRIAL SEPTAL DEFECT*

By A. D. NICHOL, M.D. *and* DON D. BRANNAN, M.D.
CLEVELAND, OHIO

IT IS probable that the experience of this audience in the identification of congenital cardiovascular lesions has been much the same as ours. Since the advent of surgical measures designed to correct, or to partially compensate for some of these defects, more patients have been available for study, and the differentiation of the various lesions has become of immediate importance. The syndromes resulting from a congenital cardiovascular lesion may be so typical that a substantially correct diagnosis can be made in a large percentage of cases. Patent ductus arteriosus and atrial septal defect can be differentiated by their clinical and roentgenological features.

An abstract of Maude Abbott's analysis of 1,000 postmortem cases[1] reveals that, as a primary lesion, patent ductus arteriosus occurred 92 times and atrial septal defect, 73 times. The defects co-existed in 16 of these 165 cases. Statistical reviews on patients attending cardiac clinics[10] have established the high incidence of congenital lesions and have emphasized the frequency of atrial septal defect as a pure lesion.[2]

Numerous reviews of the clinical and postmortem findings in patients with patent ductus arteriosus and atrial septal defect are available in the English medical literature.[2,5,8,11,12,14,15] The differentiation of these two lesions will be approached by reviewing their effects on the circulation by diagrammatic means (Fig. 1). These diagrams are modifications of many somewhat similar schemes which serve to provide a basic framework for the correlation of clinical findings. In patent ductus arteriosus (Fig. 1*A*), blood from the aorta, the highest mean pressure point of the circulatory system, is shunted to the pulmonary artery, already filled with blood. The pulmonary artery dilates to accommodate this increased volume which, on returning to the heart, causes enlargement of the left atrium. The increased filling of the left atrium, and of the left ventricle, increases the systolic output delivered to the aorta. Even though a considerable part of the left ventricular output is shunted through the ductus,[6] the peripheral flow is usually only slightly decreased. The shunt occurs between high pressure vessels, but we believe the pressure differential is sufficiently high to cause blood to flow through the ductus only from the aorta to the pul-

* From the Departments of Medicine and Radiology, St. Luke's Hospital, Cleveland, Ohio. Presented at the Mid-Western Clinical Conference of Radiology, Cleveland, Ohio, Feb. 14–15, 1947.

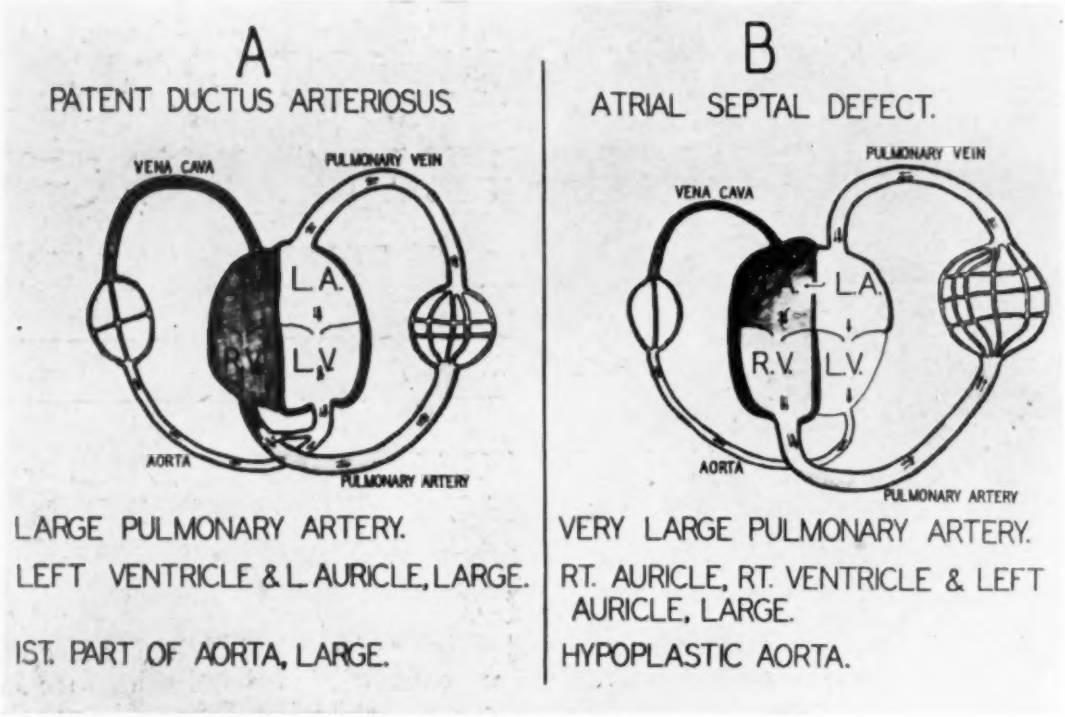

FIG. 1. Schematic diagram illustrating modification of the heart and circulation in (*A*) patent ductus arteriosus and (*B*) atrial septal defect.

monary artery. We have never seen cyanosis which could be attributed definitely to a reflux of venous blood through an uncomplicated patent ductus.

In atrial septal defect (Fig. 1*B*), the right atrium receives the peripheral venous flow and apparently, in numerous instances, a large complement of blood from the left atrium. This increased volume of blood causes great enlargement of the right atrium and right ventricle; it increases right ventricular systolic output[3] which results in considerable enlargement of the entire pulmonary vascular system. When this increased blood volume is returned to the left side of the heart, the interatrial septal defect provides an escape mechanism which prevents an otherwise extreme enlargement of the left atrium, but the run-off through the septal defect also decreases left ventricular filling. This decreased filling results in decreased left ventricular output and decreased peripheral blood flow. Although the arrow between the left and right atria points only in one direction, it is probable that slight pressure changes will cause a reversal of flow; venous blood will enter the left side of the heart and be delivered to the peripheral circulation. Careful observation or an adequate history will occasionally elicit evidence of transient slight cyanosis in infants with an interatrial septal defect.

We are not aware of proof for all of these hypotheses but their probabilities will be supported by illustrations from some of our patients who have shown the characteristic signs of patent ductus arteriosus and of atrial septal defect. Usually, a sufficient combination of these findings to establish a clinical diagnosis will be present. Pure patent ductus arteriosus or atrial septal defect can be recognized as successfully as acquired valvular heart disease.

Figure 2 is from an opacification study obtained on a girl, aged thirteen, who had patent ductus arteriosus. After diodrast injection, the right ventricle and pulmon-

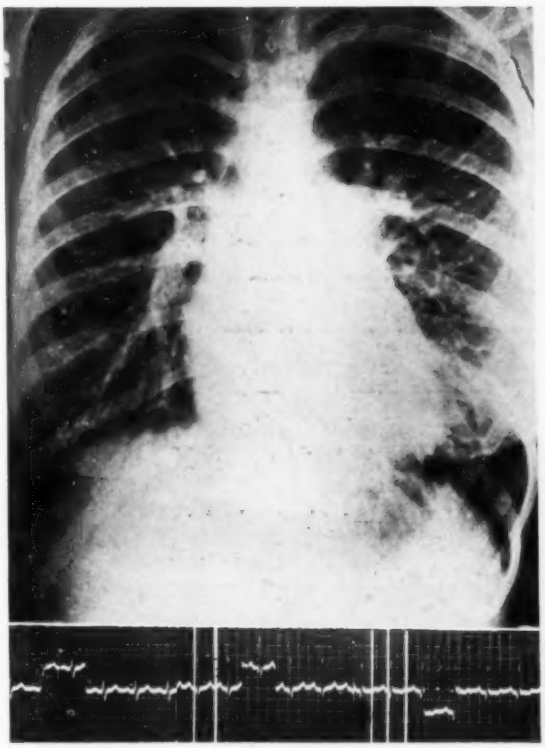

Fig. 2. Posteroanterior chest roentgenogram taken four seconds after injection of 50 cc. of 70 per cent diodrast into the left cubital vein. There is opacification of the right heart and pulmonary vessels.

ary arteries are clearly shown. The main pulmonary stem, as well as its various branches, is large and the interventricular septum lies well within the cardiac silhouette. Thus, the increased total transverse diameter is due to the relatively large size of the left ventricle; the base of the right ventricular shadow is approximately normal. We believe the aortic shadow, uninjected and well delineated from the pulmonary artery, is large for a thirteen year old female, weighing 116 pounds. Left ventricular enlargement, dilatation of the pulmonary artery and a normal or large aorta, are findings associated with patency of the ductus arteriosus. Figure 3[7] shows the blood pressure determinations of this

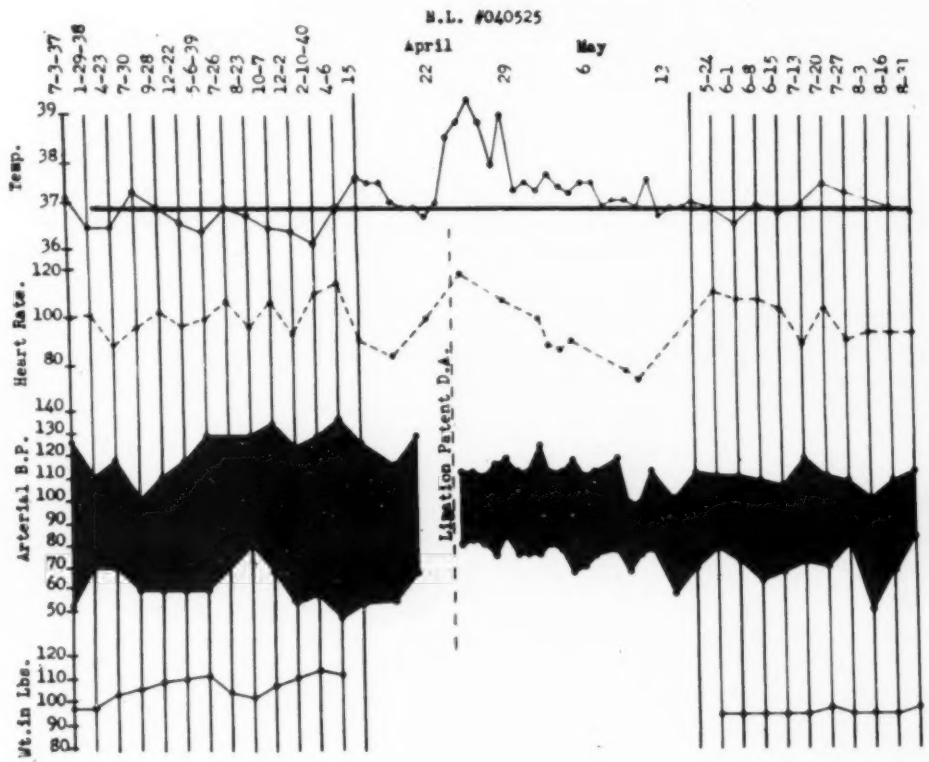

Fig. 3. Blood pressure determinations before and after ligation of a patent ductus arteriosus.

same patient. Ligation of the patent ductus was done on April 23, 1940, and there was an immediate fall in the systolic pressure and a rise in the diastolic pressure. The normal blood pressure and smaller pulse pressure obtained postoperatively are clearly demonstrated. The increased pulse pressure, resulting from patency of the ductus arteriosus, is usually not so marked as exists in an acquired left-sided arteriovenous shunt of similar size or in marked insufficiency of aortic valvular heart disease. However, this increased peripheral pulse pressure is a definite help in establishing a diagnosis of patent ductus arteriosus and particularly helpful in differentiating patent ductus arteriosus from an atrial septal defect. The electrocardiogram (Fig. 2) was essentially normal. We believe the diphasic QRS complex in Lead I represents a persistence of the infantile pattern.

Figure 4 represents roentgenograms of the chest of a female, aged thirty-seven. The relatively large aorta, the slight prominence of the pulmonary artery and the large ventricular shadow are shown in the posteroanterior projection (*A*). In addition, there is a semicircular line of calcification (arrow) in the aortic arch, superimposed upon the lower part of the aortic knob. As verified at postmortem, this shadow outlines the aortic opening of a patent ductus arteriosus. Such a finding, described by Weiss[16] is rare, but it may be helpful in establishing a diagnosis.[4] The entire aorta can be clearly seen in the lateral projection (*B*). Such an aorta is abnormally large for a frail female weighing 97 pounds. Even though the enlargement cannot be demonstrated roentgenologically, we believe the first and second portions of the aorta are always enlarged in an uncomplicated patent ductus arteriosus and the entire aorta may be abnormally prominent. The axis of the electrocardiogram was normal.

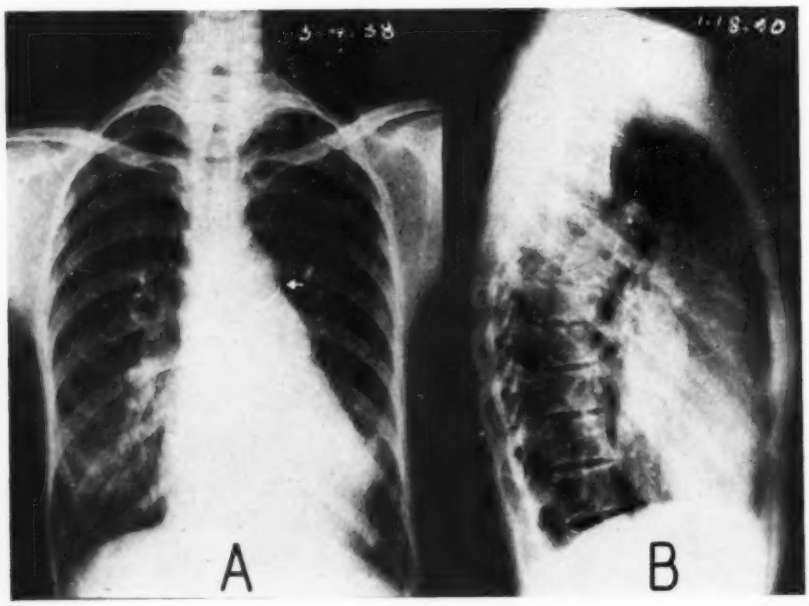

FIG. 4. Posteroanterior and lateral views of the chest showing calcification (retouched) at the aortic orifice of a patent ductus arteriosus.

Figure 5 represents two posteroanterior views of the chest of a well developed female, now forty-three years old. Her heart is slightly enlarged now (*A*), as it was when she was first seen in 1940 (*B*). The aortic knob is prominent and the ventricular mass extends posteriorly to an abnormal extent in the left oblique view (Fig. 6*B*). The pulmonary artery is slightly enlarged.

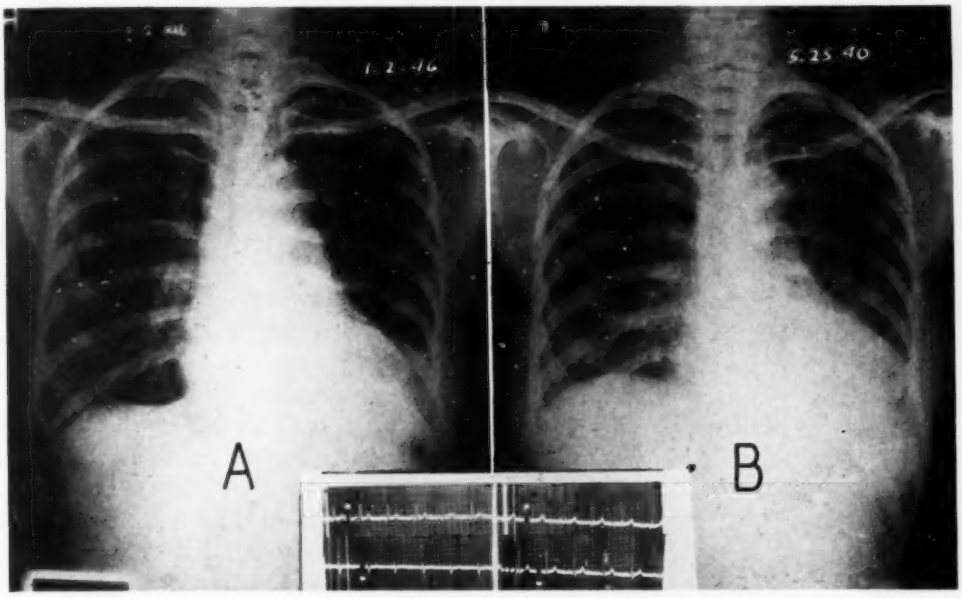

Fig. 5. Posteroanterior views of the chest of a patient with patent ductus arteriosus. There is a six year interval between these films.

This enlargement is more marked in Figure 5*A* than in Figure 5*B*, six years earlier. The right oblique projection (Fig. 6*A*) is of more assistance, as it shows a moderate prominence of the upper cardiac shadow, indicating definite enlargement of the pulmonary artery. The electrocardiogram shows a left axis deviation (Fig. 5). A continuous loud systolic and a loud blowing diastolic murmur has always been present, most often with a systolic accentuation. In addition, a very definite systolic thrill is palpable in the third left interspace corresponding to the site of the maximum

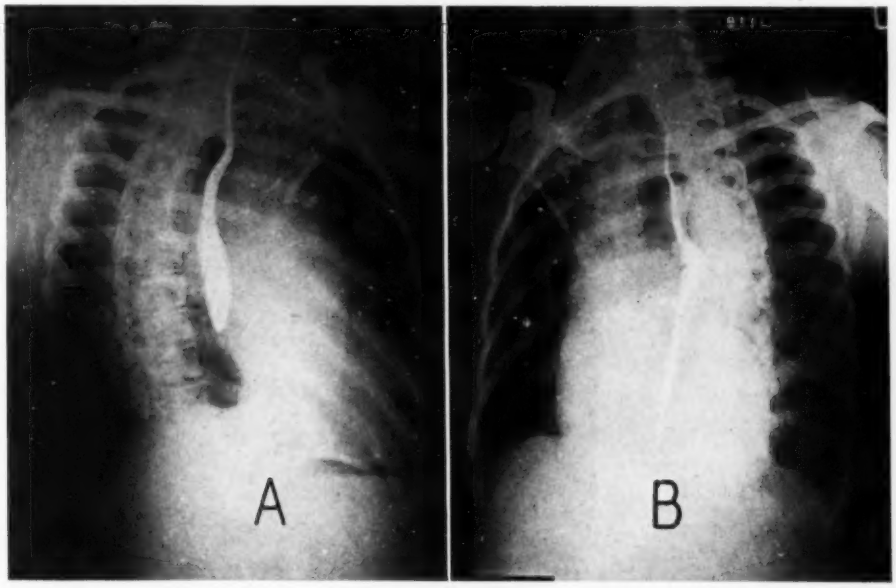

Fig. 6. Right (*A*) and left anterior oblique (*B*) views, same patient as Figure 5.

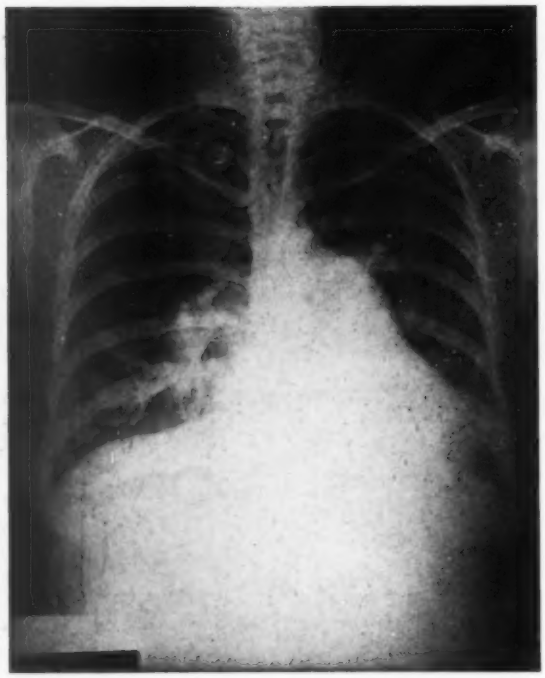

FIG. 7. Chest roentgenogram of patient with atrial septal defect.

intensity of the murmur. The patient's blood pressure is variable but an average reading is 136/80. We are reasonably sure that this patient has a patent ductus arteriorus.

Figure 7 is a posteroanterior projection of a heart with a typical atrial septal defect. The patient is a widow, aged forty-six, who was closely supervised for twenty years because of a mistaken diagnosis of rheumatic mitral stenosis. She had no symptoms of heart disease. After physical examination, our Medical Resident disagreed with the accepted diagnosis. Simultaneously, the X-ray Department suggested that the patient had an atrial septal defect. The great enlargement of the pulmonary artery and its branches and the marked enlargement of the heart are clearly shown. The aortic arch is small and there is no chronic passive hyperemia of the lungs (Fig. 7). Despite the great increase in the transverse diameter of the heart, the ventricular mass does not extend posteriorly to any considerable extent in the left oblique position (Fig. 8*B*). The right ventricle is enlarged. Under the roentgenoscope the large comma-shaped vessels in the right hilum were seen to pulsate. The retrocardiac space is clear and the esophagus is straight in the right oblique projec-

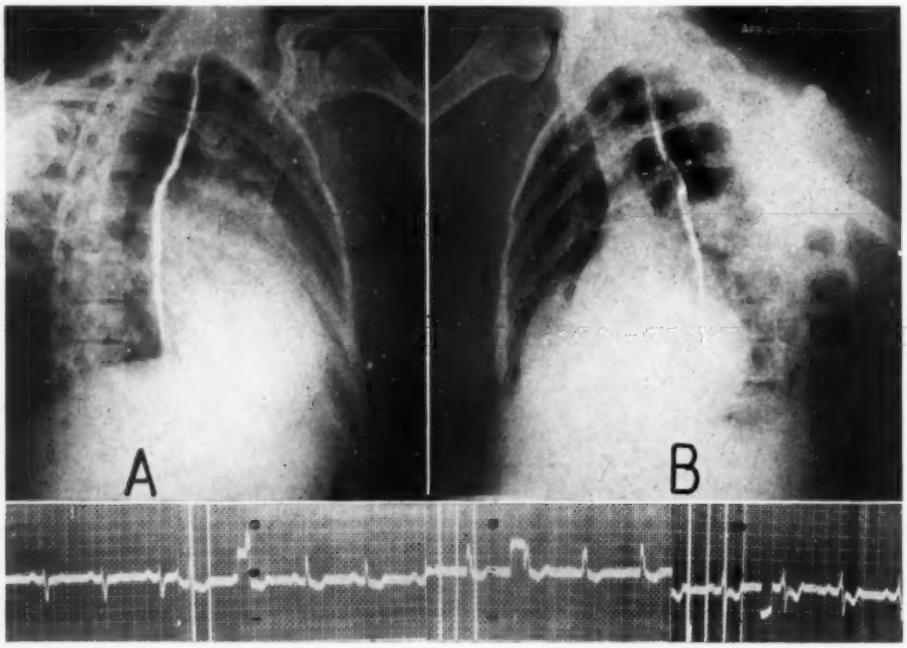

FIG. 8. Right (*A*) and left (*B*) anterior oblique views of same patient as Figure 7.

tion (Fig. 8*A*). The latter findings are particularly valuable in disproving a diagnosis of mitral stenosis. We have never seen, and find it impossible to imagine, a situation in which an uncomplicated mitral stenosis could cause excessive dilatation of the pulmonary artery and of the right heart without marked enlargement of the left atrium and consequent encroachment on the esophagus and retrocardiac space. Severe rheumatic heart disease and mitral stenosis should produce some clouding of the lung parenchyma; there should be moderate physical disability and moderate dyspnea on exertion. There is a right axis deviation of the electrocardiogram (Fig. 8). The diagnosis of atrial septal defect was finally accepted by all physicians interested in the patient. A right axis deviation of the electrocardiogram is never found in an adult with uncomplicated patent ductus arteriosus.

Figure 9 is the chest roentgenogram of a male patient, now thirty years of age. He is an asthenic individual, who was in fair health except for slight shortness of breath on exertion until he was twenty-two years old. He was then admitted to a tuberculosis sanatorium for observation because of a "large right hilar shadow." The diagnosis was changed to rheumatic heart disease with mitral stenosis and aortic insufficiency. The patient subsequently had two periods of congestive cardiac failure, apparently almost entirely right-sided. At present, he is working and comfortable, except for shortness of breath on more than moderate exertion. There is a definite prominence of the left anterior chest wall near the sternum at the level of the second, third and fourth ribs. Variable double murmurs, with the diastolic element most prominent, are present with a maximum intensity in the third left intercostal space. An average blood pressure determination is 100/76. With best health, his hemoglobin is 18.5 grams and the red blood cell count 5.99. The cardiac shadow (Fig. 9) has a large transverse diameter, a marked prominence of the right and main pulmonary arteries and an indefinite aortic arch. In the right oblique view (Fig. 10*A*), the large pulmonary artery is responsible for the increased depth of the upper cardiac shadow; the retrocardiac space remains relatively clear although there is slight indentation of the esophagus. The left oblique view (Fig. 10*B*) shows enlargement of the right ventricle and the large pulmonary artery and its branches obliterating the aortic window. The electrocardiogram (Fig. 10) has a right axis deviation and the P waves, particularly in Lead II, are abnormally tall and peaked. The evidence clearly indicates that the major defect in this patient is an atrial septal defect. It is possible that a mitral stenosis (Lutembacher's syndrome)[9] is also present.

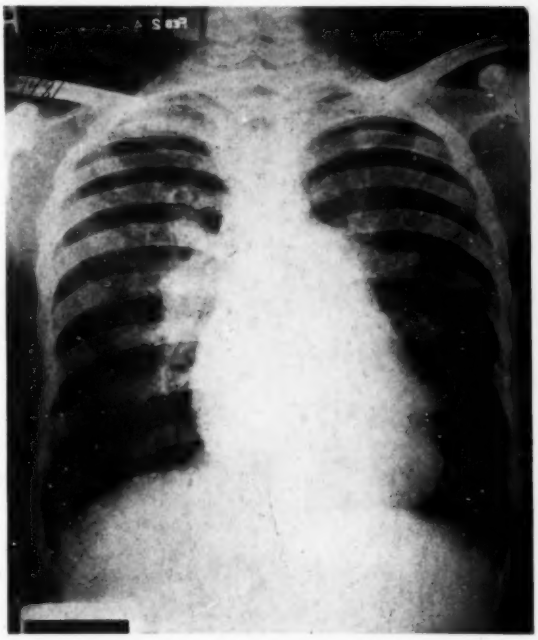

Fig. 9. Posteroanterior chest roentgenogram of patient with atrial septal defect.

Figure 11 shows in more detail some of the electrocardiographic abnormalities associated with an atrial septal defect. These records were obtained from a patient, now twenty-three years old, who has been under our observation for sixteen years. He was a frail child with associated congenital abnormalities of the osseous and muscular system. The cardiac mechanism has never

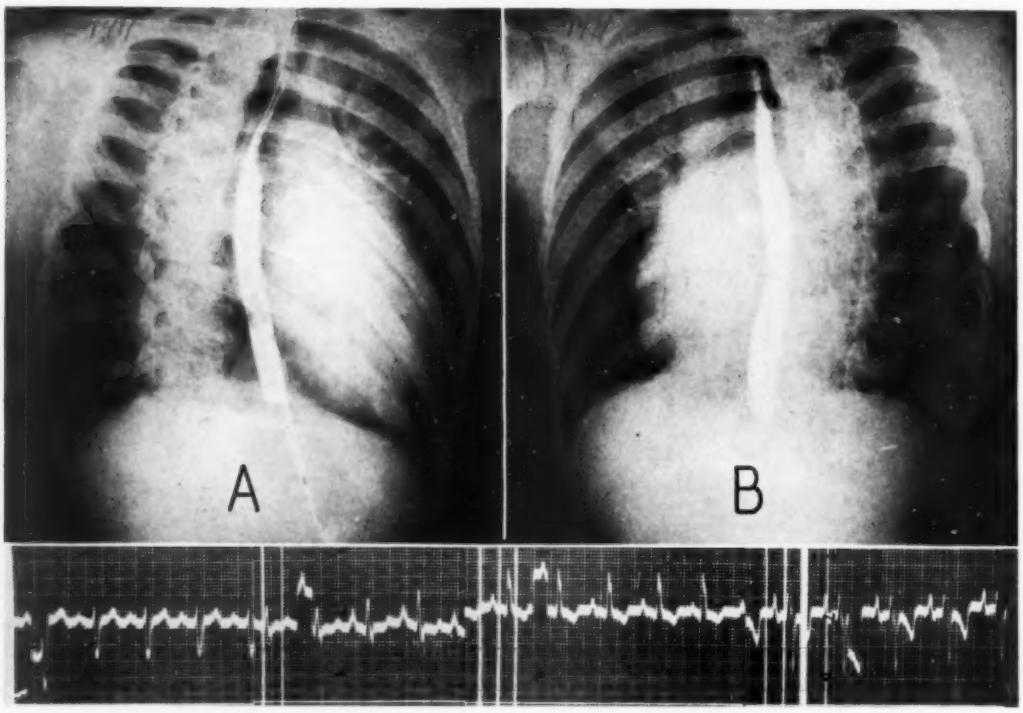

FIG. 10. Right (*A*) and left (*B*) anterior oblique views of same patient as Figure 9.

been stable, and the irregular rhythm in Figure 11*A* is due to a shifting pacemaker. In Figure 11*B*, a period of normal sinus rhythm is present, but there is a right axis deviation manifested by a deep S wave in Lead I and a tall, upright R wave in Lead III; abnormal P waves are clearly seen in Lead II.

The next case would have been handled differently if we had been more certain of our diagnostic abilities in 1940. The patient was a female, aged forty-two months. She had a double murmur without systolic accentuation and there was a definite localized prominence of the anterior left chest wall at the level of the second and third ribs. The electrocardiogram has a right axis deviation (Fig. 12). The heart shadow

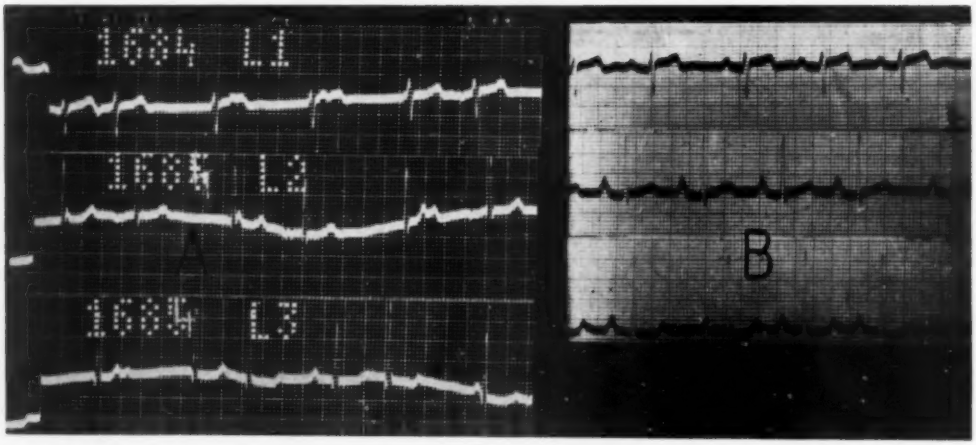

FIG. 11. Electrocardiogram showing abnormalities present with atrial septal defect.

is increased in size (Fig. 12), and the aortic arch cannot be identified. Over-exposed films (Fig. 13*A*) show the right ventricle, filled with diodrast, to represent almost the entire transverse shadow of the heart, while the prominent knob above the upper left border of the heart is clearly demonstrated to be a very large pulmonary artery. In Figure 13*B*, taken four seconds later, diodrast has filled the aorta which is smaller than the main pulmonary trunk. After considerable discussion, an exploratory operation of the chest revealed only a large, tense pulmonary artery, and no patent ductus or other abnormalities of the large vessels. The preoperative studies in retrospect clearly indicated such a probability. Now, we believe there was good clinical evidence of an atrial septal defect and operation should have been clearly contraindicated.

Table 1 represents the main factors which are important in the differentiation of these two congenital defects of the circulation. In patent ductus arteriosus, we have

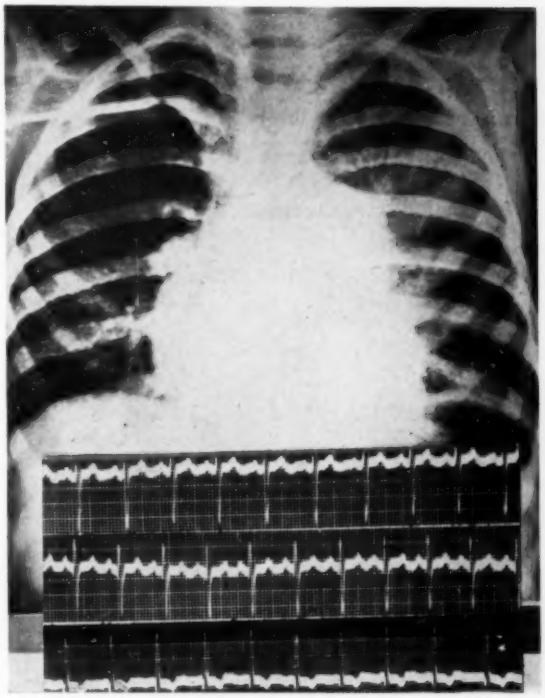

Fig. 12. Chest roentgenogram of a female, aged forty-two months, with atrial septal defect.

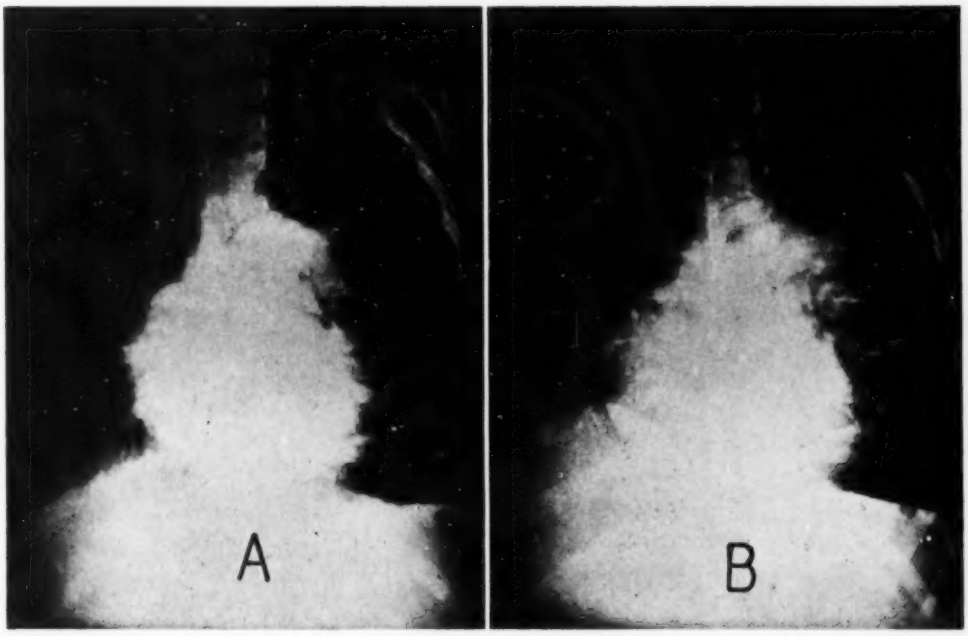

Fig. 13. Over-exposed posteroanterior chest roentgenograms made after injection of 70 per cent diodrast. The pulmonary artery is well opacified in *A* and the shadow of the aorta is accentuated in *B*.

been impressed with the absence of cyanosis, the prominent thrill and the characteristic murmurs, the essentially normal electrocardiogram with normal sinus rhythm, and on roentgen study, by the large heart with the unusual combination of ocasional slight enlargement of the left artium and definite enlargement of the left ventricle, pulmonary artery and first and second portions of the aorta. We are particularly interested in these latter findings for we believe they are responsible for some of the respiratory difficulties of infants with a patent ductus. The increased blood volume and the re-circulation through three large vessels (aorta, pulmonary artery and patent ductus arteriosus) creates an unusual mass of great vessels. The slightly large left atrium presses the tracheal bifurcation from below in a cephalad direction; a large ductus and large pulmonary arteries exert pressure posteriorly and medially to the right; the large first and second portions of the aorta have a similar tendency. As a result, tracheal deviation with compression and partial obstruction, particularly of the left main branch, occurs. In some infants, we believe such an obstruction is a factor in the frequency, persistence and severity of pulmonary infections and that the obstruction may be a cause for retardation of development in infancy. As the child grows and the tracheal bifurcation descends, relatively more space is available for upper mediastinal structures and partial tracheal obstruction is spontaneously relieved.

Of less importance in the diagnosis of patent ductus arteriosus is a localized pulsation in the second or third left interspace due to the slight-to-moderate enlargement of the pulmonary artery. An increased pulse pressure is occasionally of value in differential diagnosis. Bacterial endocarditis, when present, is presumptive evidence against an atrial septal defect. Slight circulatory insufficiency is usually present in patent ductus arteriosus, although it may not be appreciated by the patient or physician until operative closure of the ductus has been affected.

In atrial septal defect, we have been most impressed by the variability of murmurs and thrills, by the right axis deviation and abnormal P waves of the electrocardiogram which may also show an unstable cardiac conduction mechanism. The roentgen findings are of paramount importance because of the characteristic increase in the size of the heart due to the marked increase in the size of the right atrium and ventricle.

TABLE I

IMPORTANT FACTORS IN THE DIFFERENTIAL DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS AND ATRIAL SEPTAL DEFECT

Patent Ductus Arteriosus	*Atrial Septal Defect*
1. Normal development after infancy	1. Subnormal physique
2. No cyanosis	2. Minimal transient cyanosis
3. Localized pulsation in 2nd left interspace	3. Localized prominence of left anterior chest wall in region of 2nd, 3rd and 4th interspaces
4. Maximal systolic and diastolic thrills	4. Variable thrills
5. Usually typical murmurs	5. Variable murmurs
6. High systolic, low diastolic blood pressure	6. Low systolic blood pressure and narrow pulse pressure
7. Normal electrocardiogram or left axis deviation. Normal sinus rhythm	7. Right axis deviation of electrocardiogram. Large P waves. Various arrhythmias
8. Enlargement of left ventricle and left auricle. Large pulmonary artery. Large aorta	8. Enlargement of right auricle and right ventricle. Great dilatation of pulmonary artery. Hypoplastic aorta
9. Slight circulatory insufficiency	9. Congestive cardiac failure, preponderately right-sided
10. Subacute bacterial endocarditis	10. Acquired valvular heart disease

The dilatation of the pulmonary artery and its branches or the dilatation of the conus is a constant finding. In contrast, the aortic knob is small and inconspicuous.

Patients with atrial septal defect show a definite tendency to subnormal physique, particularly in infancy, but one of our patients, who was a small child with transient slight cyanosis, has developed into a semi-professional baseball pitcher with the body build of a gladiator. The localized prominence of the left anterior chest wall may be absent; occasionally, it is of great help in differentiating this lesion from patent ductus arteriosus, for this sign tends to be conspicuous in the younger age group in whom the roentgen-ray silhouette is less characteristic. These patients have a low systolic blood pressure and narrow pulse pressure; such a finding in a patient with marked enlargement of the heart is an obvious paradox. Acquired valvular heart disease, particularly a co-existing mitral stenosis, is consistent with atrial septal defect and it is interesting that bacterial endocarditis is rare. Congestive cardiac failure tends to occur late. It is almost pure right-sided failure.

The total combination of the differentiating points in Table 1 is an ideal pattern, the construction of which has been an interesting study to us. It has proved to be increasingly valuable as more attention has been centered on eliciting the various factors in individual patients.

SUMMARY

Since the advent of surgical measures to correct or modify various types of congenital heart lesions, more interest has developed in the differential diagnosis of these conditions. Two of the most common abnormalities are patent ductus arteriosus and atrial septal defect. They present sufficiently characteristic findings to enable one to make the correct clinical diagnosis in a large percentage of cases. These findings have been illustrated by cases of patent ductus arteriosus and atrial septal defect. The important features in the differential diagnosis have been presented in tabular form. We believe that the diagnosis can be made with the same exactitude as in acquired valvular heart disease.

11311 Shaker Blvd.
Cleveland 4, Ohio

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SYNDROME OF ABERRANT RIGHT SUBCLAVIAN ARTERY WITH PATENT DUCTUS ARTERIOSUS*

By HENRY P. BREAN, M.D., *and* EDWARD B. D. NEUHAUSER, M.D.
BOSTON, MASSACHUSETTS

INTRODUCTION

ABERRANT right subclavian artery is the most common of all congenital anomalies of the aortic arch. In this anomaly, the right subclavian artery takes origin from the extreme left side of the aortic arch, posteriorly and to the left of the origin of the left subclavian. The aberrant vessel runs obliquely upward and to the right, usually passing behind the esophagus as it crosses the midline. The embryologic background of this anomalous origin and course is known and is discussed below.

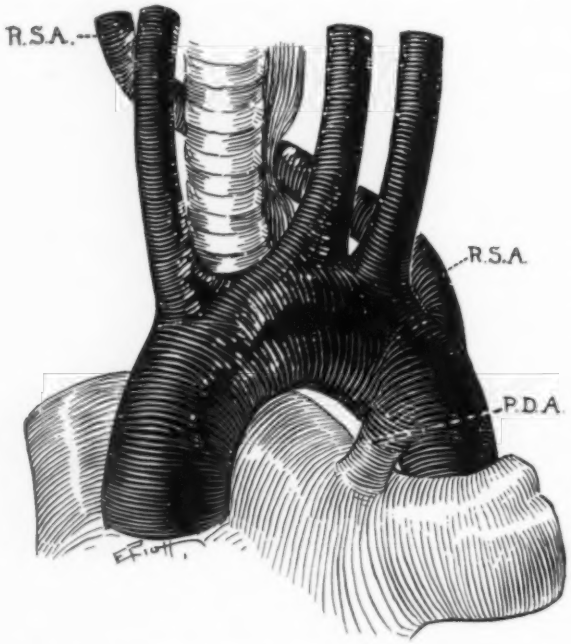

FIG. 1. Aberrant right subclavian artery with patent ductus arteriosus. Drawing of the great vessels showing the patent ductus arteriosus, *P.D.A.*, and the obliquely ascending course of the aberrant right subclavian artery, *R.S.A.*, behind the esophagus which is indented posteriorly.

The main clinical and roentgenologic features of anomalous subclavian artery are now well defined and several cases in which the roentgen diagnosis has been made have been reported.[5,12,13] However, the relatively high incidence of coexistent congenital heart disease, particularly anomalies of the cardiac base such as patent ductus arteriosus (Fig. 1) and the tetralogy of Fallot, has not been recognized. The group of cases to be reported is part of a series of 15 patients, all infants or young children, in whom the diagnosis of aberrant right subclavian artery has been made.

ANOMALOUS SUBCLAVIAN ARTERY

The clinical aspects of anomalous right subclavian artery and of other anomalies of the aortic arch have recently been reviewed by Gross and Ware.[11] The roentgen diagnosis of this vascular deformity, together with its diagnostic differentiation from posterior right aortic arch and double aortic arch, has recently been reviewed by Neuhauser[12] and by Copleman.[5]

The anomaly is often asymptomatic or associated with only mild feeding difficulty. However, it occasionally results in marked dysphagia by its extrinsic pressure on the esophagus, thus constituting a true "dysphagia lusoria." A surgical procedure to relieve the dysphagia of anomalous subclavian artery has been devised by Gross and successfully carried out in 2 cases.[11]

The characteristic course of the aberrant vessel, from its origin far to the left on the aortic arch, passing obliquely upward and to the right behind the esophagus, produces a typical oblique extrinsic filling defect in the posterior esophageal wall. Anomalous subclavian artery passing between esophagus and trachea or anterior to the trachea is uncommon and has not been encountered in this series.

* From the Department of Roentgenology, The Infants' and The Children's Hospitals and the Department of Radiology, Harvard Medical School, Boston, Massachusetts.

PATENT DUCTUS ARTERIOSUS

In every case the diagnosis must be made by adequate clinical evidence. This should include in patients beyond infancy, the characteristic systolic and diastolic "machinery murmur" in the pulmonic area, together with widened pulse pressure and some retardation of somatic growth.

Roentgenologic criteria for the diagnosis of patent ductus arteriosus are well established.[7] When present they include total cardiac enlargement, left ventricular hypertrophy, dilatation of the left atrium and prominence of the pulmonary artery segment of the cardiac shadow. The hilar and pulmonary vessels are usually engorged. The left ventricle and pulmonary artery segment show increased amplitude of pulsation and there may be visible expansile pulsation of the hilar vessels ("hilar dance"). Any or all of these signs may be lacking in any individual case.

CONGENITAL HEART DISEASE WITH ANOMALOUS SUBCLAVIAN

Fifteen cases of anomalous right subclavian artery have been discovered by roentgen examination at the Children's Hospital in the year from September, 1945 through August, 1946. Five of these children had undoubted congenital heart disease as well, 2 being surgically verified. Three of the congenitally abnormal hearts were clinically and roentgenologically typical of patent ductus arteriosus, 1 being surgically verified. The fourth was a tetralogy of Fallot, surgically verified. The fifth was a congenital abnormality of indeterminate structure, but apparently involving an intracardiac shunt.

The coexistence of a patent ductus arteriosus in 3 out of 15 patients with an aberrant right subclavian artery suggests that the two entities may be related, either by one constituting direct causation for the other, or by virtue of a common etiology and pathogenesis for both. In the light of present knowledge of the effect of certain virus infections in the first trimester of pregnancy, the latter possibility is suggested. German measles in early pregnancy is now known to be a common and potent cause of congenital heart disease, cataract, deafness and other anomalies.[6,8,9,10] In 1 of the 3 cases (Case II), a common etiology is evident; in another (Case III), a common etiology is suspected. Evidence bearing on this problem is presented in the case reports and is discussed below.

CASE REPORTS

Case 1 (Record No. 304,068). B. W., female, aged three years, seven months, entered the Medical Outpatient Department on April 11, 1946, for investigation of a previously discovered heart murmur. Her father, an electrician, aged twenty-seven, and her mother, aged twenty-three, were living and well; there were no familial diseases. No siblings. Mother denied any illness during pregnancy. Birth was full term with a normal delivery. Birth weight 7½ lb. There was no neonatal cyanosis, and development of motor activity was normal. Throughout infancy she suffered from marked difficulty in swallowing both liquid and solid food, with ready and frequent regurgitation. This decreased as she grew older, but she is still described by her parents as a slow eater. She had never had dyspnea, orthopnea, cyanosis, weak spells or edema.

Physical examination showed a thin female child, weight 27¾ lb. (average normal for age 33 lb.), temperature 99.8° F.; pulse 108. No cyanosis. Skin, head, eyes, ears, nose and throat negative. Chest shape was not abnormal and heart was not enlarged to physical examination. There was a thrill in the second and third interspaces just to the left of the sternum, with a loud blowing systolic and diastolic "machinery murmur" at this site. Rhythm regular. Blood pressure 100/60. Lungs were clear to percussion and auscultation. Abdomen, genitalia and extremities negative. No clubbing of fingers or toes.

Electrocardiogram was normal; no axis deviation present.

Roentgenographic and roentgenoscopic examination (X-ray No. A481) showed the heart at or just beyond the upper limit of normal in size with enlargement of the left ventricle and abnormal prominence of the pulmonary artery. The hilar and intrapulmonary vessels were engorged. Examination of the esophagus with barium swallow showed a well de-

fined oblique extrinsic pressure defect in the posterior esophageal wall above the aortic arch, without obstruction to barium flow. Figure 2 shows heart and aberrant subclavian defect.

Comment. This child presents the classical features of a patent ductus arteriosus—machinery murmur, slight somatic retardation, left ventricular and pulmonary artery enlargement and engorgement of hilar vessels. Routine roentgenoscopy uncovered an anomalous subclavian artery. Neither anomaly is producing important symptoms at present. Ligation and division of the ductus is planned in a year or so.

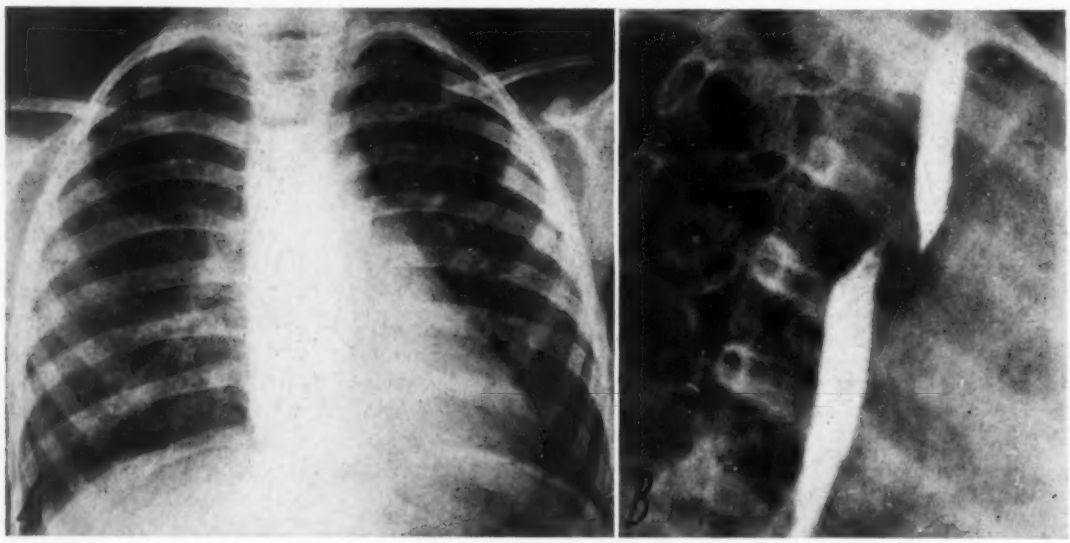

FIG. 2. Case 1. Aberrant right subclavian artery with patent ductus arteriosus. *A*, chest roentgenogram showing left ventricular enlargement, moderate prominence of the pulmonary artery segment and engorgement of hilar vessels. *B*, oblique roentgenogram of the esophagus showing the typical oblique extrinsic filling defect posteriorly above the level of the aortic arch.

CASE II (Record No. 306,660). R. S., male, aged two years, seven months, entered the Children's Hospital on June 11, 1946, because of easy fatigue and failure to gain weight. Parents living and well; a four year old sibling is normal. Pregnancy was remarkable in that the mother had German measles when two months pregnant. Birth was somewhat premature; delivery was normal. The baby was cyanotic for the first five days after birth and congenital cataract was noted. In infancy development was delayed and he was considerably underweight. In early infancy there was easy regurgitation on any but slow feeding and even at present feeding is slow. He had had three severe respiratory infections, each requiring hospitalization. Activities were partially limited by easy fatigue, but there was no dyspnea, orthopnea or edema and no cyanosis since the neonatal period.

Physical examination showed a thin and active child, quite small for his age, weighing 20½ lb. (average normal for age 29 lb.). Temperature 99.2° F., pulse 110, respirations normal. Left eye showed lenticular opacity, with tearing and conjunctival injection. No cyanosis. Skin, head, ears, nose and throat negative. Chest showed a marked precordial bulge. Heart was enlarged to percussion, with a systolic apical thrill. At the apex was a loud systolic murmur. In the pulmonic area moderately loud systolic and diastolic murmurs were heard. Rate was rapid, rhythm regular. Lungs clear to percussion and auscultation. Liver edge was felt 1½ fingerbreadths below the right costal margin. No other organs or masses palpable, but there was a small umbilical hernia. Left testis was incompletely descended and phimosis was present. Extremities negative; no clubbing present.

Urine negative. Erythrocyte count 4 million with 12.5 gm. hemoglobin. Electrocardiogram showed sinus tachycardia, rate 140, with di-

phasic QRS in all leads; duration of QRS, however, was 0.09 second, within normal limits.

Roentgenographic and roentgenoscopic examination of the heart (X-ray No. A1179) showed it markedly enlarged to the right and left. There was considerable left ventricular hypertrophy, marked enlargement of the left atrium and abnormal fullness of the pulmonary artery segment. Right atrium also appeared enlarged. Left ventricle, pulmonary artery and aortic arch showed markedly exaggerated amplitude of pulsation and the hilar vessels were engorged. Examination of the esophagus with barium swallow showed a posterior oblique extrinsic pressure defect indicative of an anomalous right subclavian artery (see Fig. 3).

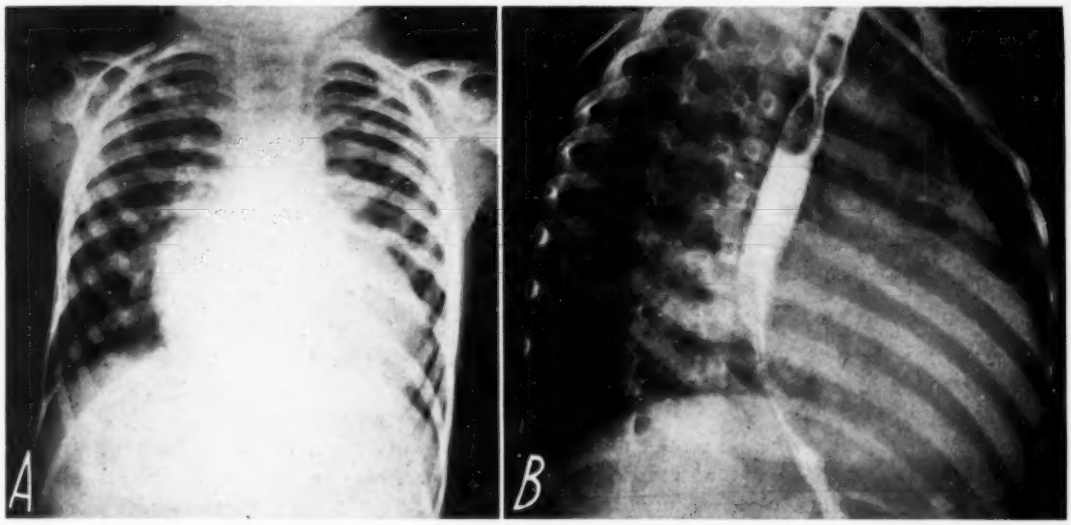

Fig. 3. Case II. Aberrant right subclavian artery with patent ductus arteriosus. *A*, chest roentgenogram showing cardiac enlargement to the right and left, left ventricular enlargement, fullness of the pulmonary artery segment and engorgement of hilar vessels. *B*, right anterior oblique roentgenogram of the esophagus showing the oblique posterior defect above the level of the aortic arch.

Operation (Dr. Robert E. Gross) revealed a large patent ductus, estimated 8 mm. in length and 8 mm. in diameter. The ductus was ligated and divided. Confirmation of the aberrant subclavian vessel by exploration of the posterior mediastinum was felt to require too extensive dissection in this rather frail child.

On the seventh postoperative day roentgenographic and roentgenoscopic re-examination showed marked decrease in rate and amplitude of pulsation, both being then within normal limits. Barium swallow again demonstrated the characteristic oblique defect of an aberrant subclavian artery.

Patient was discharged, improved, on the fifteenth hospital day.

Comment. This child, whose mother had had German measles in the second month of pregnancy, showed multiple congenital defects including congenital cataract, probable defective tear duct, umbilical hernia, undescended testis, anomalous subclavian artery and a patent ductus arteriosus. The patent ductus was associated with considerable general cardiac enlargement and was presumably partly responsible for the inadequate somatic growth. The aberrant subclavian caused only minor feeding difficulty and its presence was unsuspected before its discovery by routine roentgenoscopy.

Case III (Record No. 305,233). J. R., a female infant, aged one year, nine months, entered the Medical Outpatient Department on May 15, 1946, for investigation of a heart murmur discovered three months previously. The mother is being treated for lues, said to have been contracted from the father, a mechanic, after his return from the Armed Forces. During the second month of pregnancy the mother had a severe prolonged virus-like illness with fever and respiratory symptoms. Delivery was nor-

mal; there was no neonatal cyanosis. Motor and somatic development were normal. No actual dysphagia is known, but child is described as a "poor eater." She has had no cyanosis, dyspnea, weak spells or edema.

Physical examination showed a well developed and nourished baby girl weighing 26 lb. (normal for her age). No cyanosis. Skin, head, eyes, ears, nose and throat negative. Chest not abnormal. Heart appeared enlarged to the left. A loud blowing systolic murmur and a probable soft diastolic murmur were heard in the second interspace to the left of the sternum. No thrill palpable. Lungs were clear to percussion and auscultation. Abdomen and extremities negative. No clubbing present.

Blood Hinton test was reported negative.

Roentgenographic and roentgenoscopic examination of the heart (X-ray No. A627) showed slight total cardiac enlargement. Left ventricle and left atrium were enlarged, with marked prominence of the pulmonary artery segment. There was enlargement of the left ventricle and left atrium, with marked prominence of the pulmonary artery segment. There was strikingly exaggerated expansile pulsation of the pulmonary artery, amplitude of one border estimated at 1 cm. The hilar and pulmonary vessels were engorged. Examination of the esophagus with barium swallow revealed an oblique extrinsic pressure defect posteriorly, typical of an aberrant right subclavian artery.

Comment. This child, whose mother had a severe infection during the second month of pregnancy, had a loud systolic murmur in the pulmonic area and a probable faint diastolic as well (auscultatory findings in an infant of this age being often uncertain). There is roentgen evidence of an enlarged and markedly pulsating pulmonary artery. The ductus is probably a small one and no clinical effects are as yet evident. As in the previous 2 cases, routine roentgenoscopic examination revealed the additional roentgen picture of an aberrant subclavian vessel.

The following 2 cases are examples of congenital abnormality, other than patent ductus arteriosus, of the base of the heart and associated great vessels; each is accompanied by an anomalous subclavian artery.

CASE IV (Record No. 271,709). R. C., a male, aged four years, five months, was admitted to the Children's Hospital on December 13, 1945, because of recurrent hematemeses, five weeks in duration. He had had a previous admission in his second year because of a fractured skull followed by a right hemiplegia and gross congenital heart disease was noted as an incidental feature. There were no known familial diseases and pregnancy is not known to have been abnormal. Delivery was normal, at full term. Cyanosis was noted at birth. Cyanosis increased progressively and was constant during the past two years. Growth and development were somewhat retarded. There was no major feeding problem, but definite difficulty in swallowing full mouthfuls of semisolid foods is described.

Physical examination showed a deeply cyanotic, poorly developed male child with rapid labored respirations; temperature 98.6° F., pulse 120, respiration 50. Skin negative except for cyanosis. Head, eyes, ears, nose and throat not remarkable. Heart appeared enlarged to the right. No thrill was palpable, but there was a soft precordial systolic murmur. Lungs were clear to percussion and auscultation. Abdomen negative. Fingers and toes showed severe clubbing. Right arm was paralyzed, with a flexion deformity. Right leg weak. Reflexes elsewhere not remarkable.

Electrocardiogram showed right axis deviation. Urinalyses negative. Erythrocyte count 8.5 million. Hematocrit 74. Hemoglobin 21 grams per cent. Leukocyte count 16,700.

Roentgenographic and roentgenoscopic examination of the heart (X-ray No. 83942) showed the heart not enlarged by measurement, but with a grossly abnormal contour. The right ventricle showed considerable enlargement and there was narrowing in the left waist of the heart in the region of the pulmonary artery segment. The left ventricle also appeared enlarged and the aortic shadow was prominent. Lungs were clear. Examination of the esophagus by barium swallow showed a small oblique filling defect posteriorly at the aortic arch level, the appearance being that characteristic of an aberrant subclavian vessel (see Fig. 4).

On the eighth hospital day the patient was transferred to the Surgical Service. On the thirty-first day anastomosis of the innominate artery to the pulmonary artery was performed by Dr. Robert E. Gross. A to-and-fro murmur

in the pulmonic area appeared, cyanosis slowly decreased, polycythemia diminished and re-examination by roentgenograms and roentgenoscopy showed definite increase in the pulmonary vascular markings. Follow-up visits show a marked increase in well-being and ability to exercise.

Comment. This child presents the classic picture of the tetralogy of Fallot, confirmed by surgical exploration and markedly benefited by surgical anastomosis of the innominate artery to the pulmonary artery.

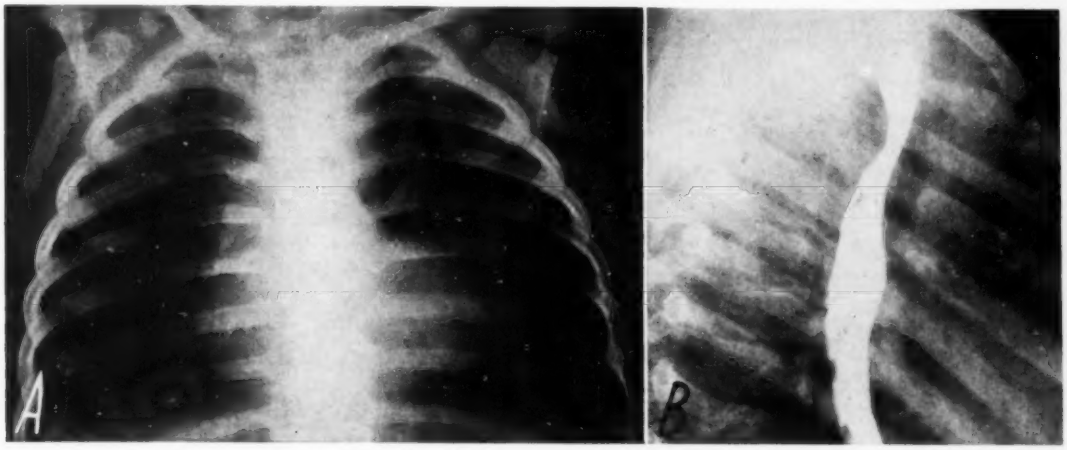

Fig. 4. Case iv. Aberrant right subclavian artery with tetralogy of Fallot. *A*, chest roentgenogram showing narrowing in pulmonary artery segment with elevation and displacement of the apex by right and left ventricular enlargement. *B*, lateral view of esophagus showing posterior defect above level of aortic arch.

An aberrant subclavian artery, which had produced mild dysphagia with solid foods, was discovered on routine roentgenoscopy.

Case v (Record No. 299,718). D. B., a female, aged four years, eleven months, entered the Children's Hospital on November 14, 1945, for evaluation of her known congenital heart disease. There were no known familial diseases and two siblings were apparently normal. Mother had no known illness during pregnancy. Delivery was at term and was uncomplicated. There was a mild neonatal cyanosis which persisted throughout the first year of life and is now noted only during crying. Growth and development were within normal limits. There was no known dysphagia. In her second year she was hospitalized for three days for an unexplained episode of severe dyspnea. No other dyspnea is known and no edema. However, there has been undue fatigue after exercise, limiting activity somewhat.

Physical examination showed a fairly well developed female child weighing 40½ lb. (normal for age), temperature 98.6° F., pulse 90, respiration 24. No cyanosis. Skin, head, ears, eyes, nose and throat not remarkable. Chest normal in shape, except for questionable fullness over the precordium. There was a very loud basal systolic murmur with thrill; no diastolic heard. A2 and P2 were greatly diminished. Blood pressure 110/60. Lungs were clear to percussion and auscultation. Abdomen, genitalia and extremities were negative; no definite clubbing seen.

Urinalysis negative. Erythrocyte count 4.89 million; leukocyte count 5,400. Electrocardiogram showed right axis deviation.

Roentgenographic and roentgenoscopic examination of the heart (X-ray No. 97453) showed the heart at the upper limit of normal in size. The base of the heart was unusually wide, with a prominent pulmonary artery segment. The base of the heart showed widely expansile pulsation bilaterally, but the pulmonary artery showed a quiet beat. Examination of the esophagus with barium swallow revealed an oblique defect posteriorly characteristic of an anomalous subclavian artery (see Fig. 5).

Patient was discharged, without surgical therapy, on the third hospital day.

Comment. This child presents congenital

heart disease of uncertain structure. The cyanosis on effort, loud basal murmur and right axis deviation suggest an intracardiac shunt and the absent or diminished second sound in the pulmonic and aortic area suggest that the shunt lies somewhere at the base of the heart, perhaps at the origin of the pulmonary artery and aorta. However, from the roentgenologic picture an interauricular defeat could not be ruled out. Whatever the defect, it was believed that it is not one at present amenable to surgery and exploration was not done. An asymptomatic aberrant subclavian artery was discovered during routine roentgenoscopy.

tus arteriosus. In addition, one example of the tetralogy of Fallot was seen and one congenital heart of indeterminate structure perhaps involving a basal intracardiac shunt.

Coexistent defects other than cardiac also occur. One patient (Case 11), with history of German measles in the mother in the second fetal month, showed multiple minor congenital abnormalities in addition to the aberrant subclavian and a patent ductus. Anomalous right subclavian artery may now be added to the growing list of congenital defects known to follow maternal German measles in early pregnancy.

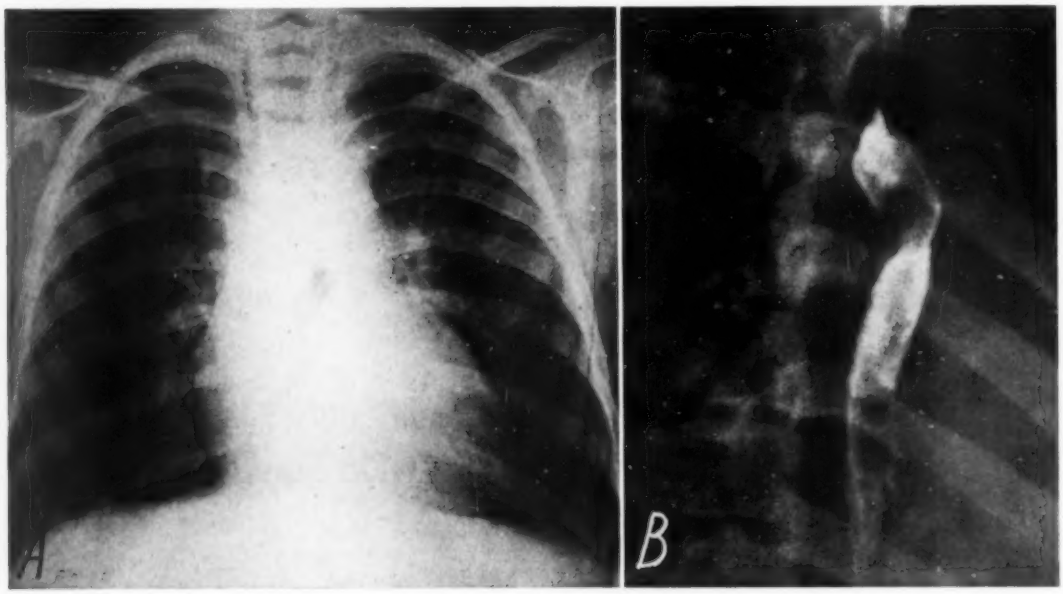

FIG. 5. Case v. Aberrant right subclavian artery with congenital heart disease of undetermined type. *A*, chest roentgenogram showing abnormal widening of mediastinal shadow at base of heart and prominence of the pulmonary artery segment. *B*, right anterior oblique view of the esophagus showing the characteristic oblique defect posteriorly above the level of the aortic arch.

DISCUSSION

Anomalous subclavian artery, previously known as an isolated congenital deformity, apparently often occurs as one of several congenital defects, particularly congenital heart disease. These are usually abnormalities of the great vessels in or at the base of the heart. In the present series the deformity was most commonly a patent duc-

The combination of aberrant subclavian artery with congenital abnormality of the great vessels at the base of the heart is apparently a common one. The embryologic significance of this syndrome is not entirely certain. The embryologic mechanism involved in the formation of anomalous subclavian artery is well understood.[1] In the transformation of the aortic arches during the second fetal month, the

fourth arch is normally absorbed just proximal to its junction with the dorsal aorta; the remainder of the arch becomes the normal right subclavian.[4] In the anomaly, the proximal portion of the arch is resorbed instead; the portion of the arch which joined the dorsal aorta then constitutes the anomalous subclavian vessel.

In the case of the tetralogy of Fallot accompanying the anomalous subclavian, it is reasonable to suppose that both defects arose from the same disturbance of embryologic development. The dextroposed aorta, pulmonic stenosis and interventricular septal defect must have been produced at the same time as the aberrant subclavian artery; namely, in the second fetal month, during the processes of aortic arch transformation, differentiation of pulmonary artery and ventral aorta and development of the cardiac septa.

In the case of patent ductus arteriosus, however, there is no evidence to suggest that fetal abnormality during the second fetal month influences the complex process of closure of the ductus normally initiated at birth. Only a few of the factors in normal ductus closure are known.[2] Tension and torsion produced in the ductus region by the anomalous subclavian origin might conceivably exert a mechanical effect on the ductus. However, it appears improbable that a mechanical factor alone could prevent the subintimal connective tissue proliferation that constitutes normal ductus closure.[3] Impaired neonatal oxygenation has been recently invoked as one cause of persistent patency of the ductus arteriosus, but it is difficult to conceive that the mere presence of an aberrant subclavian artery could significantly affect neonatal oxygenation.

The embryologic relations between anomalous subclavian artery and patent ductus arteriosus therefore remain uncertain. Although the mechanism is not known, it is difficult to believe that the two processes are entirely coincidental. It is far more probable that they are both manifestations of a basic fetal abnormality, induced in at least some cases by virus disease in the early months of pregnancy.

SUMMARY

Anomalous right subclavian artery in infants is often accompanied by congenital anomalies of the great vessels at the base of the heart. Five cases of this syndrome are reported; three were cases of patent ductus arteriosus; one, a tetralogy of Fallot; and one, a congenital cardiac anomaly of uncertain structure.

In one of the cases of anomalous subclavian artery with patent ductus arterio-sus, German measles in the mother in the second month of pregnancy was the evident cause of the congenital abnormalities.

The roentgenologic features of anomalous right subclavian artery, and of patent ductus arteriosus are reviewed. The value of a routine barium swallow during roentgenoscopic examination of the heart and lungs is emphasized.

Children's Hospital
300 Longwood Ave.
Boston 15, Mass.

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Vol. 58, No. 6

ROENTGENOLOGIC PULMONARY MANIFESTATIONS OF FATAL HISTOPLASMOSIS*

By JOHN F. HOLT, M.D.
ANN ARBOR, MICHIGAN

IN RECENT years, various investigators[1,5,7,8,11,12] have suggested that the pathogenic fungus, *Histoplasma capsulatum*, is the cause of certain instances of calcification occurring within the lungs and mediastinal lymph nodes. Although final proof of this hypothesis is not yet available, the basic significance of the observation as it now stands should not be minimized. Anyone who has attempted to rationalize repeated negative tuberculin reactions in patients with unmistakable roentgen signs of hilar and parenchymal calcium deposits can best appreciate the implications of this noteworthy contribution.

As we await additional information regarding the true role played by *Histoplasma capsulatum* in the production of clinically unimportant intrathoracic calcium deposits, it is perhaps well to recall that histoplasmosis can be a serious and frequently fatal disease involving the lungs, any or all of the abdominal viscera, the skin, the mucous membranes, the lymph nodes, the bone marrow and occasionally other portions of the body.[4] Furthermore the disease appears to be increasing in frequency—at least in certain areas. Parsons and Zarafonetis,[9] in a comprehensive review of the subject, tabulated 71 cases, 54 of which occurred between 1938 and 1943; this despite the fact that Darling[3] first described the disease in 1905. The great majority of the cases reviewed proved fatal, 56 were autopsied and, of this group, 34 had demonstrable pulmonary lesions.

Histoplasmosis is notoriously difficult to diagnose by clinical methods, and therefore it is logical to search for some reliable roentgenologic clue which might serve to identify the process more accurately. As pulmonary involvement is such a common manifestation of the disease, the attention is naturally directed toward the roentgenogram of the chest.

Nine patients with histoplasmosis which eventually proved fatal were seen at the University of Michigan Hospital between 1938 and 1946, and 5 of them had definite pulmonary involvement proved by autopsy. Four of these patients have been reported elsewhere by Parsons and Zarafonetis,[9] Kemper and Bloom,[6] Seabury and Drygas,[10] and Curtis and Grekin.[2] It was thought that a supplementary presentation of the chest roentgenograms of this group of patients might be of some interest from the diagnostic viewpoint, especially since no reproductions of roentgenograms were utilized in the previous publications. Only brief case summaries of these patients are included. For more complete clinical and laboratory data concerning them, the interested reader is referred to the articles mentioned above.

One patient (Case v) is reported herein for the first time.

CASE REPORTS

CASE I. A. J. W., a white male, aged forty-one, entered University Hospital on August 6, 1940, having as his chief complaints fever and weakness. He gave a history of having had swelling of his neck which his local physician had found to be due to enlarged lymph nodes. These allegedly had responded promptly to roentgen therapy, but weakness and lassitude had persisted.

On physical examination, a few small cervical and axillary lymph nodes were felt, the liver and spleen were found to be enlarged and widespread rales were heard in both lungs. A tentative diagnosis of lymphoblastoma was made.

Roentgenograms of the chest on August 8, 1940, showed bilateral hilar adenopathy and

* From the Department of Roentgenology, University of Michigan, Ann Arbor, Michigan.

widespread fine granular lesions in both lungs (Fig. 1*A*). Parenchymal involvement was most pronounced in the perihilar regions. The findings were thought to be compatible with the clinical diagnosis of lymphoblastoma.

Review of a histologic section made from a lymph node removed at another hospital showed lymphoblastoma of the lymphosarcoma type.

Between August 8 and August 20, 1940, the patient received 400 roentgens to each of eight fields around the chest and in the retroperitoneal region, but his condition grew progressively worse and death occurred on August 26, 1940. Re-examination of the chest (bedside roentgenogram) two days before death showed increase in prominence of the hilar shadows. The previously described fine granular lesions in the lung now appeared as considerably larger patches of parenchymal infiltration widely disseminated throughout both lungs (Fig. 1*B*).

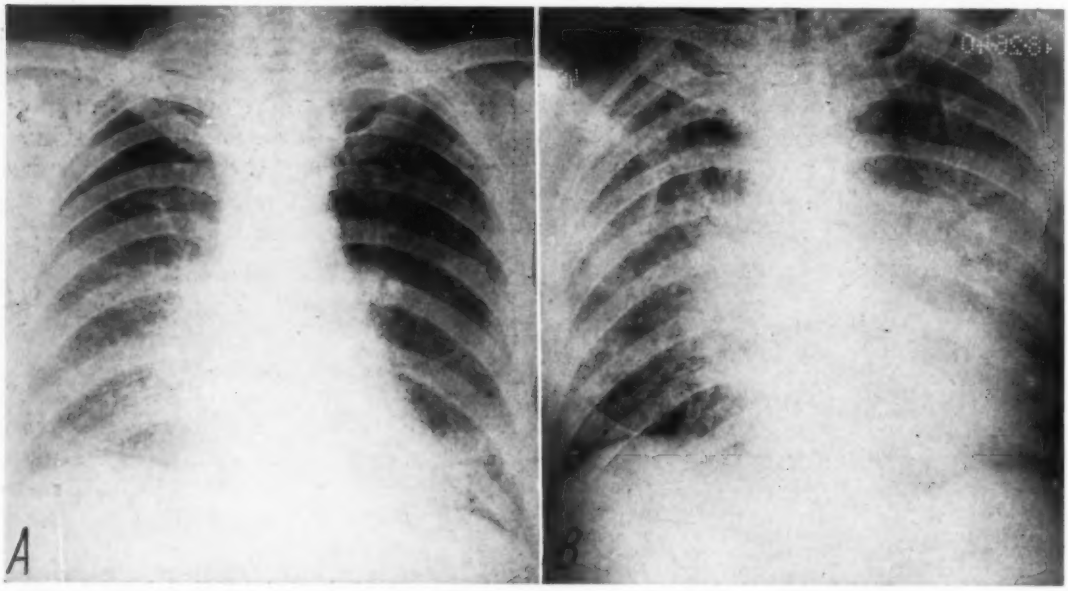

FIG. 1. Case 1. *A*, bilateral miliary parenchymal lesions and hilar adenopathy of indeterminate etiology. *B*, marked extension of pulmonary abnormalities two days before death. Autopsy showed histoplasmosis.

At autopsy, there was evidence of widespread subacute pneumonitis, acute pulmonary abscesses, chronic pulmonary edema and an acute fibrinopurulent exacerbation of chronic bronchitis. Numerous small encapsulated organisms morphologically like *Histoplasma capsulatum* were found within large mononuclear phagocytes in the alveoli. There was also involvement of bronchial lymph nodes, liver, adrenals, stomach, ileum, appendix and bone marrow. Nothing was found to support the antemortem diagnosis of lymphosarcoma.

CASE II. M. K., a white male, aged sixty, was admitted to the University Hospital on January 18, 1943, for treatment of an indolent ulcer on his tongue. Roentgenograms of the chest taken on January 23, 1943, were negative, but in March patchy pneumonitis was observed in the right lower and right middle lobes (Fig. 2*A*). This cleared within the space of a few weeks, but was supplanted by a similar process at the base of the left lung. On June 1, 1943, chest roentgenograms showed granular pneumonitis in the lower portions of both lungs, especially the right (Fig. 2*B*). In the meantime, the ulcer on the patient's tongue became larger, and additional granulomatous lesions developed in the pharynx and larynx producing severe dysphagia and complete aphonia. The patient's general condition continued to grow progressively worse and death occurred on July 16, 1943.

At autopsy, multiple fine nodular lesions were grossly observed throughout both lungs. A fibrous nodule, 1 cm. in diameter, was found in the right upper lobe, and a small area of atelectasis was seen in the right lower lobe. Microscopically, most of the fine nodular lesions appeared to be small, irregular masses

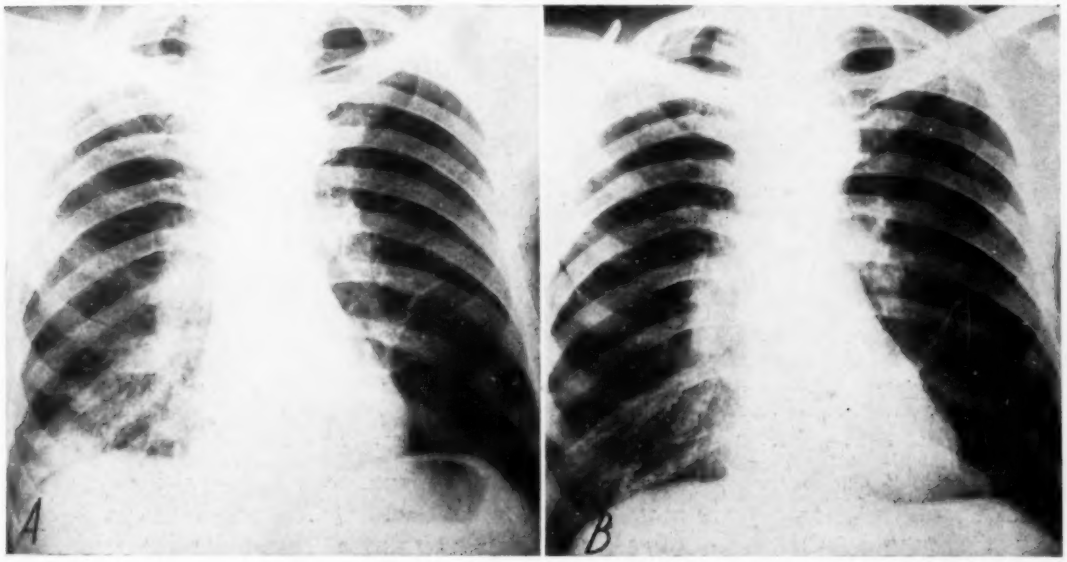

Fig. 2. Case II. *A*, patchy pneumonitis at right base which regressed and later recurred in the form of coarse granular lesions shown in *B*. Note curvilinear scar in left lung. Autopsy showed bilateral histoplasmosis.

of connective tissue containing considerable anthracotic pigment. A few well circumscribed nodules consisted of large mononuclear phagocytes surrounded by lymphocytes, and in the center of these lesions giant cells were found. An occasional *Histoplasma capsulatum* was identified in both the phagocytes and the giant cells.

Additional organisms were found in the heart, the bone marrow and the ulcerating lesions of the mouth and throat.

Case III. R. Y., a white male, aged fifty-five, first entered the hospital on June 2, 1943, complaining of perineal pain on defecation, and recent chills and fever. A partial gastrectomy had been done elsewhere in January, 1943, for suspected gastric ulcers; pathologic diagnosis made from the operative specimen was "subacute purulent gastritis."

A barium enema and sigmoidoscopy on June 7, 1943, showed narrowing and irregularity of the rectum due to an extraluminal mass. When histopathologic examination of a biopsy specimen showed no evidence of neoplasm the patient was discharged and treated conservatively by his local physician with excellent temporary results.

Recurrence of the patient's chills and fever accompanied by cough and sputum prompted him to return to the hospital on December 8, 1944. On this occasion, chest roentgenograms showed extensive solidification of the base of the right upper lobe, the over-all appearance suggesting unresolved pneumonia (Fig. 3). Barium administered by mouth outlined a persistent deformity of the lower esophagus and the upper three-fourths of the stomach, indicating the presence of either an infiltrating neoplasm or some constricting extra-alimentary mass. Barium enema showed the previously

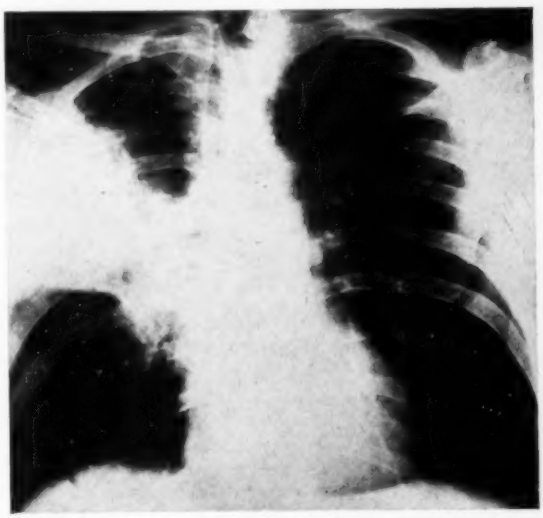

Fig. 3. Case III. Solidification of base of right upper lobe due to histoplasmosis which eventually proved fatal.

described rectal narrowing to have completely disappeared.

Bronchoscopy on December 22, 1944, was negative. The patient's condition rapidly became worse and death occurred on December 24, 1944.

Autopsy was done and histoplasmosis was found involving the right lung, liver, spleen, kidney and bone marrow. There was a severe paraesophagitis with partial obstruction of the lower esophagus but no obvious involvement of the stomach. The residuum of an old perirectal abscess was identified.

CASE IV. F. F., a white female, aged thirty, was admitted to the hospital on September 11, 1944. Her outstanding symptoms consisted of a productive cough, fever, weight loss and multiple ulcerating soft tissue swellings of the forehead, neck and the extremities. Physical findings referable to the chest included dullness to percussion at the base of the right lung anteriorly, and rales at both lung bases. The provisional clinical diagnosis on September 12, 1944, when the patient was first referred to the Department of Roentgenology was blastomycosis.

Stereoscopic frontal and single lateral roentgenograms of the chest showed right hilar adenopathy, faint, patchy pneumonitis of the right lung and questionable additional pneumonitis of the left lung. The etiology of these changes was considered indeterminate. Review of roentgenograms exposed at another hospital showed the chest to be normal in appearance on January 20, 1944, and March 7, 1944. Another chest roentgenogram from the same source dated April 20, 1944, showed minimal right hilar lymph node enlargement and questionable patchy parenchymal infiltration in the lower half of the right lung.

Biopsies of leg and scalp ulcers on September 13 and 19, 1944, were reported as showing a chronic infective granuloma, and, although no definite diagnosis was made from the biopsies, histoplasmosis was suggested as a strong possibility.

Considerable regression of the right hilar adenopathy and the bilateral pneumonitis was observed on University Hospital roentgenograms of October 17, 1944 (Fig. 4*A*), and there was now evidence of linear atelectasis at the base of the right lung suggesting subdiaphragmatic abnormality. These linear shadows persisted on check-up examinations of November 7, 1944, and January 22, 1945.

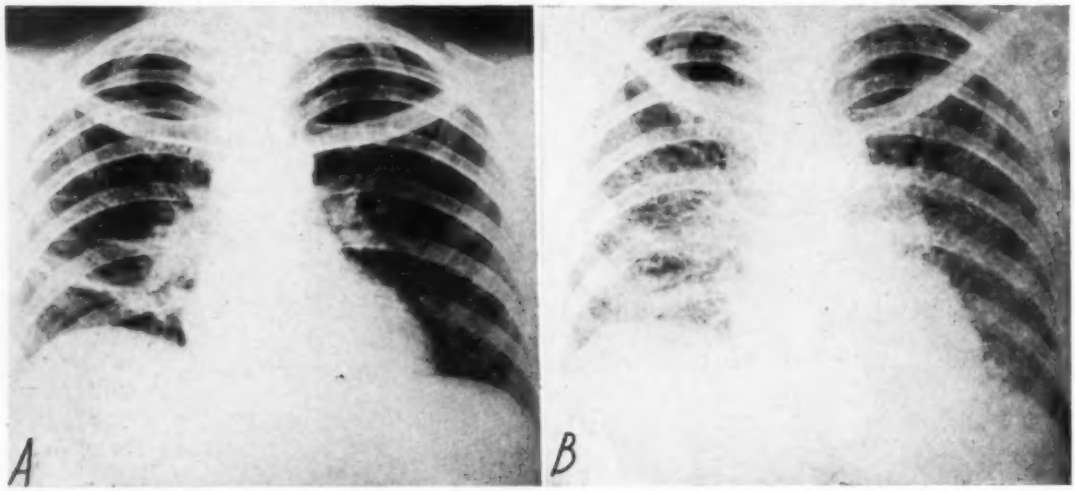

FIG. 4. Case IV. *A*, linear densities in right lower lobe thought to be due to atelectasis. Residual right hilar adenopathy. *B*, persistence of linear densities at right base and widespread dissemination of granular lesions throughout both lungs. Both histoplasmosis and tuberculosis were found at autopsy.

The patient was readmitted to the hospital on February 24, 1945, with increase in the severity of her original symptoms and with the additional finding of mild clubbing of the fingers. Chest roentgenograms on this date showed a remarkable change when compared with previous roentgenograms. Multiple areas of increased density were seen widely disseminated throughout both lungs from the apices to the

bases. In some regions the lesions appeared small, discrete and granular; elsewhere they were larger and poorly defined (Fig. 4*B*). The roentgenographic picture was not thought to be characteristic of any single disease entity, but the diagnosis became evident on the following day (February 25, 1945) when direct examination of the patient's sputum showed intracellular *Histoplasma capsulatum*. It is also of interest to note that inoculation of a guinea pig with the patient's sputum eventually resulted in isolation of acid-fast bacilli typical of *Mycobacterium tuberculosis*.

foci. The organisms of *Histoplasma* were also found in the brain, liver, spleen, bone marrow and oviducts.

Case v. M. L. H., a white male, aged forty-two, entered University Hospital on April 28, 1945, on the service of Dr. H. M. Pollard. The patient's chief complaint was fever. He gave a history of a chronic cough of five years' duration which only during the past year had been productive of mucoid sputum. Two weeks prior to his admission to University Hospital, he developed pain and stiffness in the back of his neck.

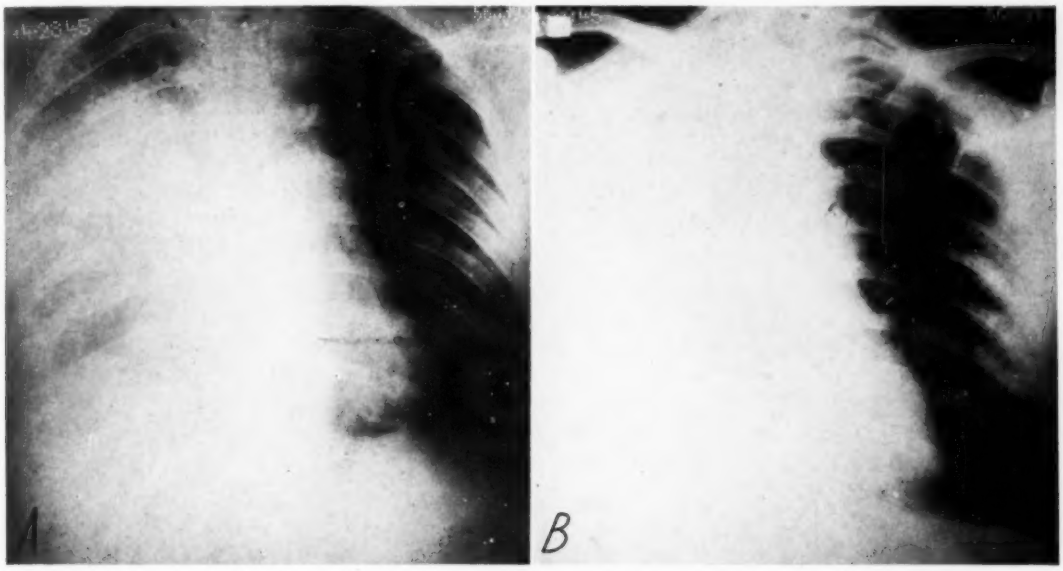

Fig. 5. Case v. *A*, extensive abnormality of right lung associated with moderate pleural fluid accumulation on the same side. *B*, two days later. Right hemithorax now completely obscured by homogeneous increase in density, presumably massive effusion. Autopsy showed complete consolidation of the right lung resulting from histoplasmosis.

Death occurred on March 3, 1945, and autopsy revealed widespread histoplasmosis and tuberculosis. Gross examination of the lungs showed "innumerable, small, miliary-sized grayish-white, firm lesions" extensively distributed bilaterally. Numerous small cavities were found in both lungs. Microscopically, there was "very extensive granulomatous pneumonitis with extensive foci of caseation necrosis surrounded by epithelioid cells." In addition there was diffuse exudative and productive pneumonitis extending over large areas. Multinucleated giant cells occurred in a few of the lesions but none of these foci closely resembled tubercles. *Histoplasma capsulatum* was present in enormous numbers in the granulomatous

This was accompanied by shaking chills, nausea, vomiting and hallucinations.

Physical examination showed a semi-comatose, irrational man whose temperature was 103.6° F., pulse 124, respirations 22 and blood pressure 128/72. There was questionable nuchal rigidity but no papilledema. The right side of the chest was flat to percussion, decreased breath sounds were heard beneath the right clavicle and coarse, moist rales were present over the entire left lung. There was no clubbing of the fingers.

The urine examination showed 2+ albumin and occasional red and white blood cells. The blood count was within normal limits. Blood Kahn reaction was negative. Repeated sputum

examination showed numerous cocci; no acid-fast organisms. Serosanguineous fluid obtained by thoracentesis was cultured, but only an organism of the *Hemophilus* group was grown. Agglutination tests for typhoid, paratyphoid and brucella were negative.

A bedside roentgenogram of the chest made the same day the patient entered the hospital showed a poorly defined, somewhat rounded area of abnormal parenchymal density in the right upper lung (Fig. 5*A*). This area measured about 12 cm. in diameter, and there was questionable evidence of cavitation in its center. The lower portion of the right lung was partially obliterated by a homogeneous shadow of increased density. The findings were thought to be most suggestive of a right upper lobe lung abscess with associated pleural fluid accumulation on the right. Patchy pneumonitis was seen in the lower portion of the left lung. Two days later, another roentgenogram showed complete obliteration of the right hemithorax. This was thought to be due to massive pleural fluid accumulation, although the possibilities of massive consolidation or atelectasis of the right lung were also considered (Fig. 5*B*).

The final clinical diagnosis was chronic pulmonary granuloma of indeterminate etiology with toxic psychosis and meningismus. The patient remained in an agitated type of coma and death occurred on May 5, 1945.

Autopsy showed histoplasmosis of the lungs, lymph nodes, liver, spleen and adrenals. The right lung was completely consolidated and the left lung contained numerous nodules measuring 4 to 12 mm. in diameter as well as a larger area in the left lower lobe which appeared somewhat caseous. Microscopic sections showed "widespread seropurulent and necrotizing pneumonitis with caseation necrosis in some areas. There is no tubercle formation, and staining for acid-fast organisms has been consistently negative. Around the borders of the caseous areas there are numerous macrophages with basophilic inclusions which are believed to be *Histoplasma capsulatum*."

COMMENT

It is evident, in our limited experience, that an antemortem diagnosis of pulmonary histoplasmosis based solely upon roentgenologic findings has not been possible. A quick perusal of the chest roentgenograms reproduced in Figures 1 to 5 will show that a more diversified group of pulmonary changes scarcely could be found in any disease or group of diseases even if one deliberately attempted to do so. Although very few illustrations of chest roentgenograms showing pulmonary histoplasmosis appear in the medical literature, a review of various authors' descriptions of roentgenographic findings in their respective case reports clearly indicates that our own antemortem diagnostic difficulties have been in no way unusual. Perhaps the most consistent finding has been the occurrence of widespread granular lesions extensively disseminated throughout both lungs such as were seen in Cases I and IV. This miliary spread is usually a terminal manifestation, however, and is of little help in diagnosing the early stages of the disease. Furthermore, it is well known that disseminated granular lesions in the lung are notoriously difficult to classify roentgenologically. Thus one can merely add this form of histoplasmosis to the differential diagnosis of a long list of disease entities which includes miliary tuberculosis, pneumoconiosis, sarcoidosis, lymphoblastoma, bronchopneumonia, lymphogenous pulmonary metastases, numerous fungus infections and many other conditions.

It has been well established that histoplasmosis and tuberculosis occur together relatively frequently, and there is ample evidence to indicate conclusively that both diseases will produce cavitation in the lung. These facts obviously make the problem of diagnosis even more difficult than would otherwise be the case. This is well exemplified by our Case IV. *Histoplasma capsulatum* was observed in a direct smear of the patient's sputum six days before death, and *Mycobacterium tuberculosis* was isolated several weeks post-partum from a guinea pig which had been inoculated with the same sputum. Autopsy showed multiple cavities and numerous organisms of *Histoplasma* in the patient's lungs, but neither definite tubercles nor tubercle bacilli were found in these structures.

Although histoplasmosis affects persons

of all ages, its relatively high incidence in the fifth, sixth and seventh decades of life makes differentiation from bronchogenic neoplasm a difficult problem for the roentgenologist. This is particularly true when the disease manifests itself as in Case III or Case V. Although the clinical signs and symptoms in these patients were not indicative of neoplasm, the roentgenologic findings were so suggestive of this abnormality that bronchoscopy was required for more accurate evaluation.

SUMMARY

The roentgenologic pulmonary findings as well as brief clinical and pathologic reports of five patients with fatal generalized histoplasmosis are presented. One of these cases is reported for the first time; the others are included as a roentgenologic supplement to previous University of Michigan publications.[2,6,9,10] Analysis of the findings in these five patients indicates that the pulmonary changes in histoplasmosis are fully as varied as the clinical manifestations of the disease. Thus histoplasmosis belongs to that relatively large group of pulmonary diseases in which the roentgenologist must be content to identify the presence of abnormality, to determine its extent, to describe certain features regarding its appearance, and to offer various suggestions regarding its etiology without arriving at a definite diagnosis. The possibility of *Histoplasma capsulatum* as the etiologic agent of chronic pneumonitis should be particularly mentioned when widespread, coarse, granular, parenchymal lesions are encountered.

Final diagnosis of histoplasmosis depends upon various laboratory procedures all of which are directed toward identification of the causative organism—a yeast-like fungus characteristically found in the cells of the reticulo-endothelial system.

University Hospital
Ann Arbor, Mich.

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THINNESS OF PARIETAL BONES

REPORT OF A CASE HAVING PREDOMINANTLY UNILATERAL INVOLVEMENT

By ANGUS K. WILSON, M.D.
SALT LAKE CITY, UTAH

SINCE the reports by Camp and Nash[1] and by the author,[4] there have been no contributions to the literature dealing with this subject. Inasmuch as the condition is bilateral and symmetrical in the majority of cases, and because there have been no publications referring particularly to unilateral thinness, the following case is reported.

The patient was a white male, aged eighty-eight, employed at the time of his injury in loading ice. While waiting on a customer everything suddenly "went black" and he collapsed, fell from the side of the platform on which he was working a distance of about 4 feet to the ground and received a stellate scalp wound on the left side of his skull in the posterior parietal region. On admission to St. Mark's Hospital he was unconscious but partially recovered in a short time and by the following day was mentally clear.

Inquiry relative to the body systems elicited no admission of abnormality of any nature. The only admitted past illness was the removal of a small "skin cancer" from the dorsum of his left hand in 1944; no sections were made. There was no evidence of regional metastasis or of local recurrence.

Blood pressure was 160/88. Temperature, pulse and respiration were normal on admission and during his stay in hospital. The eyes showed some A-V niching and minimal silver-wire streaking of the vessels. He had a small umbilical hernia; bilateral indirect inguinal herniae were controlled by a truss. The prostate was enlarged to about double normal size but was soft and smooth. Neurological investigation showed complete left nerve deafness, but the cranial system was otherwise normal. The biceps, triceps, patellar and Achilles reflexes were increased on the right side. A positive right Babinski on admission became negative three days later. Hoffman, abdominal, cremasteric, Gordon and Oppenheim reflexes were absent. The grip of the right hand was slightly less strong than the left, There was no interference with light touch, pain, temperature, vibratory or proprioceptive sensations.

In addition to the stellate left parietal scalp wound, there was flattening of the right parietal area of the skull. This presented, to palpation, as an indentation to the right of the midline.

The margins were smooth, its dimensions were approximately 3 by 5 cm., and one gained the impression of a firm bony floor through the overlying soft tissues. There was no tenderness to palpation and the color and texture of the overlying skin were the same as elsewhere in the scalp.

Laboratory investigations showed no abnormal findings other than an occasional epithelial cell and occasional granular casts in voided urine. The erythrocyte count was 4,290,000; leukocyte count 8,600; hemoglobin 13.0 grams; the differential white count was normal. Alkaline and acid phosphatase were respectively 7 and 3 Bodansky units. Inorganic phosphorus was 4.0 mg. and blood calcium was 10.45 mg.

Roentgen examination of the skull (Fig. 1 and 2) showed no evidence of fracture. On the right side in the parietal region, about 4 cm. from the midline, there was a shallow excavation which measured about 3 by 5 cm. It was seen best in the fronto-occipital projection but was also discernible in lateral view. Its margins were smooth, its floor approached but did not invade the inner table, and there was no evidence of roughness or of bone particles in the overlying soft tissues or within the cranium. The scalp margin, opposite the depression, was smooth and very slightly indented; the thickness of soft tissues was very slightly greater over the involved area than on the opposite side. In the corresponding region on the left side there was barely perceptible flattening but the definite saucerization seen on the right was not present.

Studies of the dorsal and lumbar spine showed extensive osteophyte formation and almost complete fusion of the twelfth dorsal and first lumbar vertebrae. The abdominal blood vessels showed arteriosclerotic calcification. Nothing suggestive of abnormality due to injury, inflammation or neoplasm was seen.

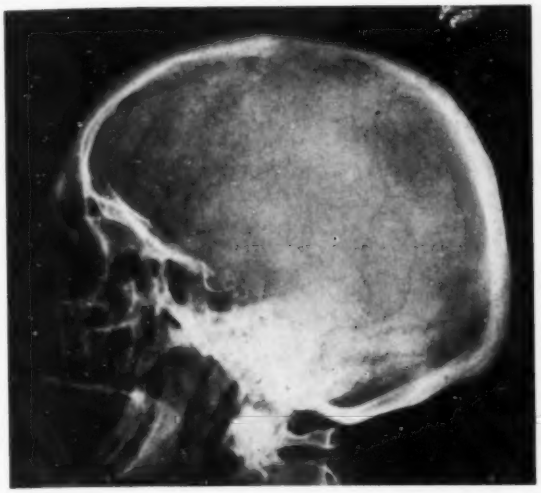

FIG. 1. Right lateral roentgenogram of skull showing radiolucent area just posterior to coronal suture line.

The patient was admitted to the hospital on March 15, 1946 at 2:30 P.M. and discharged on March 21, 1946, at 10:00 A.M. His chief complaint of dizziness on admission gradually cleared during the hospital stay. Wound healing was prompt and uncomplicated, and at the time of discharge he was in good physical condition, but because of the nature of his injury and his age he was advised to remain off work for two weeks. The discharge impression was (*a*) hypertensive arteriosclerosis, (*b*) benign prostatic hypertrophy, (*c*) umbilical hernia, (*d*) bilateral indirect inguinal herniae, (*e*) traumatic laceration of scalp from a fall judged to be due to a cerebral accident, (*f*) thinness of right parietal bone.

COMMENT

Unilateral thinness of the parietal bone is much less common than bilateral. Camp and Nash found 8 examples in the 119 cases which they reported. According to Sauvage[3] the involvement is not always exactly symmetrical, and in cases showing differences, the thinness is generally more marked on the right side than on the left. The left side involvement in the case presently reported was so slight as to be barely discernible.

The etiology of this condition is still obscure and in light of our present knowledge the dysplasia theory advanced by Greig[2] is the most plausible. It is to be noted that blood studies in this case were within normal limits, hence an actively destructive bone process is unlikely.

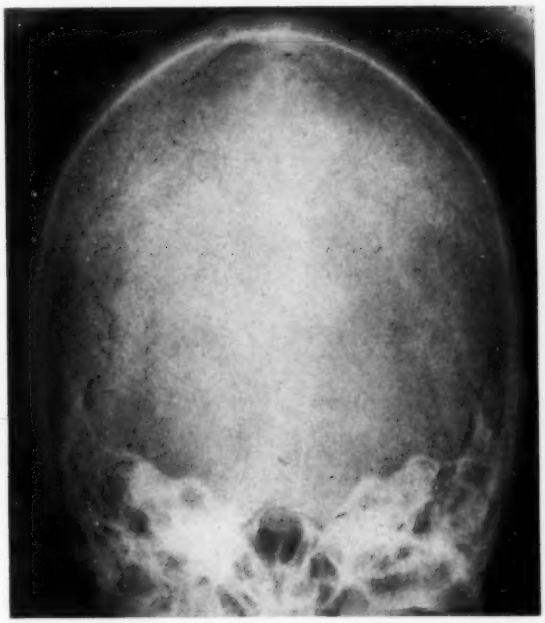

FIG. 2. Basal projection (fronto-occipital) showing saucer-like depression.

I believe the reasoning of Camp and Nash to be sound, and agree with them that until we have more exact knowledge of etiological factors, the condition should be designated simply as "parietal thinness."

The author is indebted to Drs. Paul A. Pemberton and J. E. Day, attending physicians, for permission to report this case; to Drs. S. A. Wright and S. T. Mullican for neurological and physical investigations; and to Dr. Orin A. Ogilvie for laboratory studies.

343 South Main St.
Salt Lake City 1, Utah

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VARIATIONS IN THE POSITION OF THE AZYGOS SEPTUM AND ITS INCIDENCE IN FIFTY THOUSAND ROENTGEN EXAMINATIONS

By LEWIS E. ETTER, M.D.*
PITTSBURGH, PENNSYLVANIA

SOME attention has been given to a division of the right upper lobe of the lung in the anatomical and roentgenological literature.[1,5,7,11,15] This division caused by an aberrant position of the azygos vein and the pleural coverings adjacent to it has generally been considered an anomaly of lobation and therefore called the azygos lobe. But the dividing partition or septum is made up of four thicknesses of pleura, two layers each of parietal and visceral pleura, unlike an ordinary lung septum which is composed of only two layers of visceral pleura. It is supplied by a division of the eparterial bronchus and not by a separate branch from a main bronchus as in the case of the true lobes. It is therefore an anomaly of septation rather than of lobation. However, roentgenologically, the appearance is that of an accessory lobe and it has been so generally considered.

To the septum Hjelm and Hultén[6] applied the term meso-azygos and the curved linear shadow at the right apex was first shown by Bendick and Wessler[2] and confirmed at autopsy to be the meso-azygos. This curvilinear shadow had been described previously[14] but its significance was not understood. A clear description of the anatomical features is given by Underwood and Tattersall[13] essentially as follows: In fetal life the vena azygos major courses up

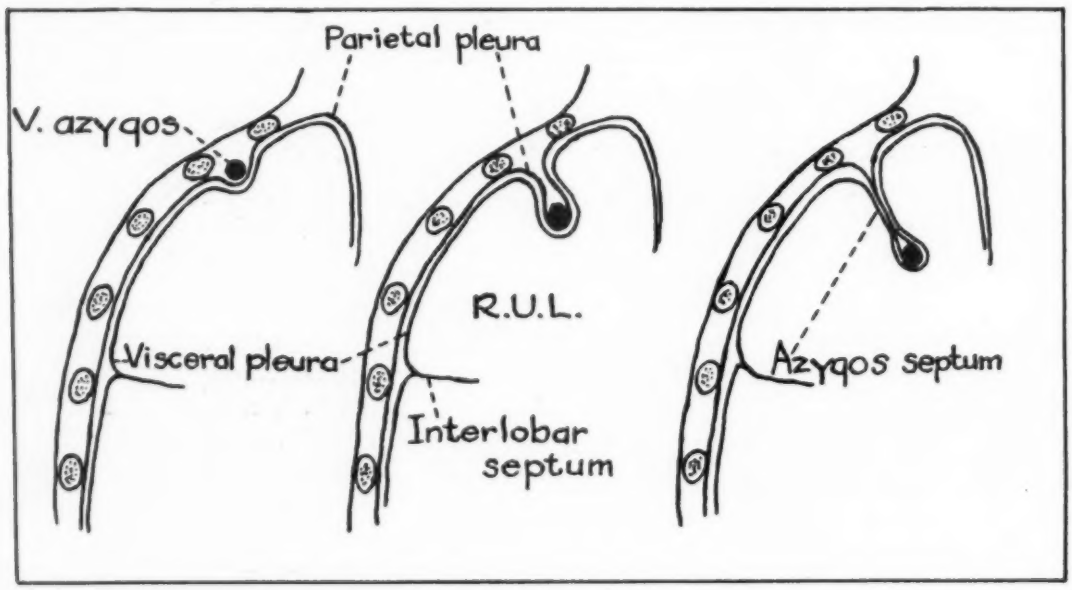

FIG. 1. Diagrammatic representation of the stages in the development of the azygos septum by invagination of the parietal and visceral pleurae by the azygos vein, resulting in formation of a septum having four distinct layers of pleura as contrasted with the true interlobar septum which has only two layers of visceral pleura. Note that the septum is lined with parietal pleura and covered externally by visceral pleura.

* Roentgenologist, Western State Psychiatric Institute and Clinic, University of Pittsburgh Medical Center.

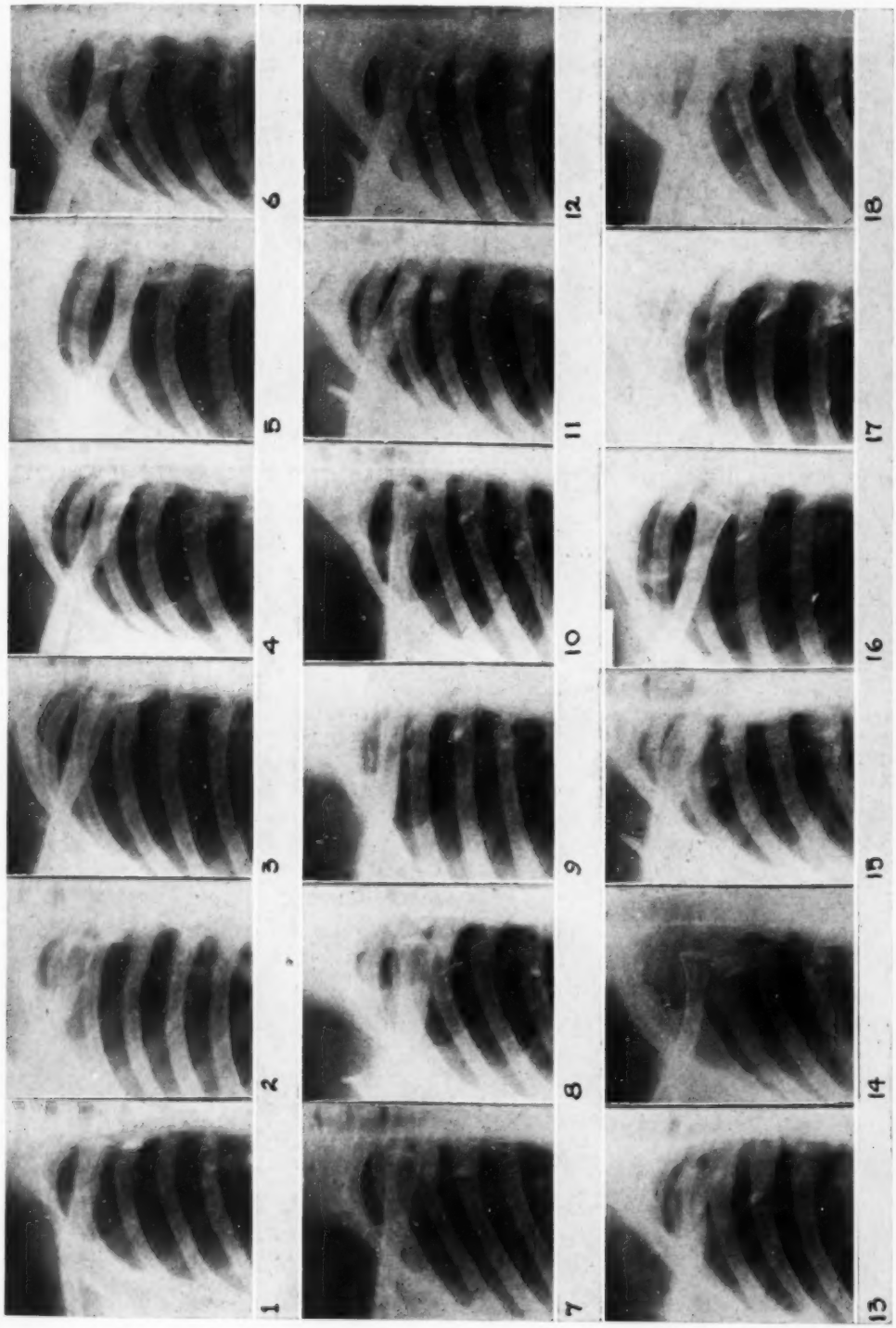

FIG. 2. Reproductions of photoroentgenograms showing extremes of variation in position of the azygos vein and septum. In the top row are shown paramediastinal positions with the septum and vein easily confused with mediastinal structures; in the middle row the more typical medial position with the well-known "comma" or "tear-drop" appearance of the vein, and in the bottom row lateral positions of the septum with atypical falciform shadows of the vein. Film No. 16 shows the septum having appearance of a thickened strand in a case of reinfection phase tuberculosis of the right apex.

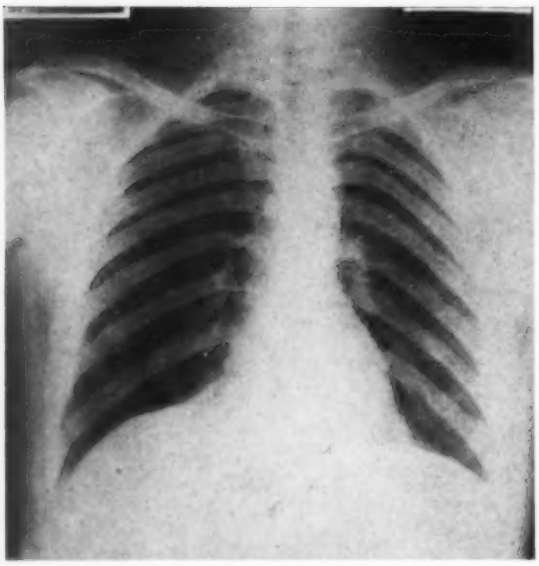

FIG. 3. Azygos septum in paramediastinal position having the appearance of a mediastinal mass.

the posterior mediastinum and arches over the root of the right lung to enter the superior vena cava on its posterior aspect. When, abnormally, the lung except the root lies more lateral, the vein instead of pursuing a vertical course in its lower portion, runs more laterally so that it cuts into the apex of the right lung and then turns medially to enter the superior vena cava on its lateral aspect. Normally the junction between the two veins lies at about the level of the second anterior intercostal space but the abnormally placed vein usually enters the vena cava at a higher level about the plane of the first interspace. The azygos vein normally lies outside both layers of the pleurae and carries with it when displaced forward into its abnormal position in the thorax both the visceral and parietal layers. As the vein pushes inward there is then formed a septum in the lung lined with two layers of parietal pleura (Fig. 1). The vein lies in the pocket formed at the base of the septum and, as can be seen in the roentgenograms shown herewith (Fig. 2), may have a variety of configuration from that of the typical "tear-drop" or "comma" shape to a rod or falciform shadow.

In this series of 50,000 consecutive roentgen examinations† a marked variation in the position of the vein and septum was observed. It was seen to vary from as far lateral as the outer third of the right thorax to a position so close to the right mediastinal border as to be scarcely distinguished from it (Fig. 2, *2*, *3*, *4*, *5*). In one case, in the medial position, the appearance required its differentiation from a mediastinal mass (Fig. 3). Debré and Mignon,[3] observing this appearance in children, called attention to the fact that it must not be wrongly considered an enlarged thymus. A very dense shadow of the vein in the paramediastinal position may be mistaken for calcification; likewise, in 2 cases (Fig. 2, *16*, and Fig. 4) the appearance of the septum was that of a thickened strand in reinfection phase tuberculosis. Friedman[4] states that the azygos septum appears denser than the adjacent lung and must not be confused with thickened pleura. Stibbe[12] divided the position of the septum in 22 cases studied by dissection into: (*a*) more or less horizontal

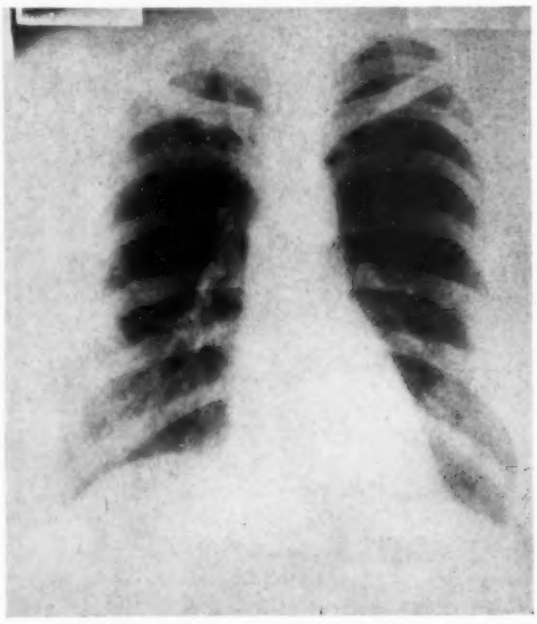

FIG. 4. Thickened azygos septum simulating strands of reinfection phase tuberculosis.

† From Armed Forces Induction Station, Altoona, Pa., 1943–1944.

cutting the lung at a point between the apex and 1 or 2 inches below it, (*b*) more nearly vertical thus dividing the apex into two more or less equal portions and (*c*) vertical, cutting off a small tongue-shaped lobe from the mediastinal surface of the upper lobe of the lung. The frequencies of these positions he found to be (*a*) 40.9 per cent, (*b*) 31.8 per cent, (*c*) 27.3 per cent. Most roentgenologists are accustomed to thinking of the typical mid-apical position with the dense tear-drop appearance of the vein at the base, and may miss a tenuous falciform shape such as shown in Figure 2, *2*, *3*, *4*, *5*, considering it to be a fibrous strand.

The frequency of azygos lobes (septums) has been given as low as 0.07 per cent (6 in 8,000 examinations) by Litten[9] to as high as 0.82 per cent (8 in 887 examinations) by Lévy and Cade.[8] Minehart[10] reported 13 in 10,000, or 0.13 per cent. The incidence of this anomaly in the variety of positions described above was found in this series of 50,000 consecutive examinations to be 130 (0.26 per cent) or 1 in 384 chest examinations. From these figures it will be seen that the occurrence is fairly infrequent and one may go for some days in a busy hospital practice before discovering an aberrant azygos vein and septum.

SUMMARY

Attention has been drawn to the fact that an aberrant position of the azygos vein produces an anomaly of septation rather than of lobation of the lung. The azygos septum is composed of two layers each of parietal and visceral pleura, unlike the ordinary lung septum which is formed of two visceral layers. Also against its being a true lobe is the fact that it is not supplied by a primary branch from the right main bronchus but rather by a twig of the eparterial stem of the bronchus to the right upper lobe. Examples have been given of a wide variety in position and form that the azygos septum may assume. Finally the incidence of azygos septation of 1 in 384 chests examined of a total of fifty thousand has been compared with the reports of others, none of which included more than ten thousand examinations, and likely represents a true index of the number to be encountered in routine studies.

Pinewood Farm
Warrendale, Pa.

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ROENTGENOGRAPHIC VISUALIZATION OF THE PLACENTA IN THE THIRD STAGE OF LABOR

A PRELIMINARY REPORT

By DAVID ROBINSON, M.D.,* *and* WILLIAM S. BOYD, M.D.†
University Hospital
AUGUSTA, GEORGIA

IN RECENT years, the roentgenographic visualization of the placenta has received more and more attention as to its significance in the diagnosis and treatment of certain obstetrical difficulties. Several techniques have been developed for roentgenographic visualization of the placenta, some of which have been rather practical; although the chances for error in diagnosis remain great, even in the hands of the more experienced roentgenologists.

The significance of the position of the placenta in utero in certain pathological conditions is too well established to need elaboration at this time. However, many points relative to the placenta such as its relationship to the fetal position and its mechanism of detachment and expulsion from the uterus are not too well understood, and therefore need further study and clarification. A preliminary report on a technique for visualization of the placenta in utero following the second stage of labor is offered with the hope that it may aid in the study of placentation and in the search for the perfect technique of placental visualization. We believe that the technique described is immediately applicable in the diagnosis of placenta accreta.

Torpin[11] showed the placenta attached to the relatively flat anterior or posterior uterine wall, with a new method of studying placentation. He found that the placentas seldom extend over the dividing line between the anterior and posterior wall, either laterally or over the apex of the fundus.

Until 1930, very little was offered from the roentgenological standpoint to the field of obstetrics. In 1932, Ehrhardt[4] and Katsuya,[5] working independently, used thorium dioxide in animals with a resulting visualization of the liver and spleen as well as the placenta. These workers advised against the use of thorium salts in humans. Lewisohn[6] used the same substance in humans and showed it to have an affinity for the reticulo-endothelial system. Stewart Einhorn and Illick[10] reported unfavorable reactions following the use of thorotrast (thorium dioxide). The work of these investigators has been borne out, and the use of thorium as a contrast medium in roentgenography is now strongly contraindicated due to its radioactivity, its affinity for the reticulo-endothelial system and the prolonged retention of the drug in the tissues.

Campbell, Miller, Menees and Holly[2] injected a water soluble contrast medium consisting of strontium iodide directly into the amniotic cavity of patients near term. Their procedure consisted in passing the needle through the abdominal wall and uterus into the amniotic cavity. The dye was then injected and roentgenograms taken. The placenta was visualized indirectly by the shadow made through the displacement of the surrounding opaque dye. They claim that reports of high death rates from this procedure were due to sodium iodide, and suggested the use of strongium iodide as a safe procedure. However, were the contrast medium safe, the dangers in amniography are still present; namely, perforation of viscera, trauma to the fetus, and early separation of the placenta due to hemorrhage.

In 1934, Ude, Weum and Urner[12] described their technique of indirect placentography. This consisted of studying the size, shape, and space between the pos-

* Department of Radiology, University Hospital (University of Georgia School of Medicine), Augusta, Georgia.
† Department of Obstetrics and Gynecology, University Hospital (University of Georgia School of Medicine), Augusta, Georgia.

terior wall of the bladder, previously injected with a solution of sodium iodide and the lower margin of the presenting fetal head. Since the initial investigations of these workers. others have shown fairly good results with their technique. Even so, the procedure is not very satisfactory in other than vertex presentations.

From time to time various radiologists have reported visualization of the placenta on conventional roentgenograms. In 1940, Dippel and Brown[3] reviewed the subject of placental visualization by roentgenography and presented an excellent paper on their technique of direct visualization of the placenta by soft tissue roentgenography They utilized factors for soft tissue technique and obtained very good results. Their work was confirmed by later workers including Baylin and Lambeth[1] and Smith[9] in 1943, and Scheetz, Good and Hunt[8] in 1945. These later workers added more information to the original work of Dippel and Brown, either by modifying their technique or combining the direct with the indirect method of visualization.

In 1941, Lloyd and Samuel[7] presented a series of 5 cases in which they were successful in demonstrating the placental site adequately by tomography. However, no further studies have been reported on their technique.

The ideal contrast medium for placental visualization would be one that could be administered either orally or parenterally which would have no deleterious effects on the fetus or the mother and cause neither premature labor nor toxic residual effects after the examination, yet give a satisfactory prepartum visualization of the placenta. The technique described here does not offer the ideal in placental visualization, but it does offer the possibility of assisting in the study of placentation.

Following delivery of the infant, there is a short period before the placenta is separated from the uterus. This period may vary normally from ten minutes to an hour; however, inasmuch as this time is not constant, the shorter period must be assumed for this technique. A sterile, water soluble radiopaque dye (diodrast compound solution, 35 per cent weight volume Winthrop) is injected into the umbilical artery, after the fetus is delivered and the cord ligated. Films of the abdomen, anteroposterior view are made and a placentogram thus obtained.

Technique. Coordination between the obstetrical and radiological services is imperative since adequate time and forewarning is necessary in order to prepare for the examination. A urological table with a Potter-Bucky diaphragm is arranged as an obstetrical table in the delivery room. Portable roentgen-ray apparatus is used, the factors being 77.8 kv. (peak), 15 ma., 2 seconds and 30 inch target-film distance. (Since multiparas have a shorter and less predictable course of labor, a primipara of small dimensions was selected for our initial examination.) Observing the usual aseptic technique, a sterile syringe containing 20 cc. of diodrast solution is held in readiness for use by the obstetrician.

Following the delivery of the infant, the cord is cleansed with alcohol, the umbilical artery is identified and the needle of the syringe is inserted into it about 6 inches from the infant's umbilicus. A small amount of blood is withdrawn to confirm the location of the needle, the cord is then clamped and ligated and the infant taken over by an assistant. The dye is injected slowly with a moderate amount of pressure 20 cc. being given in about thirty seconds. As the dye is injected, the patient is brought into position, and approximately one minute after the delivery of the infant, a roentgenogram is taken. This is followed by roentgenograms at three and five minute intervals.

The placentogram (Fig. 1) taken one minute postpartum shows a fairly circular placental shadow lying en face with some evidence of concentration of the dye within the placental tissue. The placental shadow measures approximately 14 cm. in diameter and is surrounded by a less opaque shadow which outlines the uterus. The outer limits of the uterine shadow extend about 1.7 cm. from the margin of the

FIG. 1. Placentogram.

placenta. One-half of the placento-uterine shadow lies above the iliac crests and reaches the level of the second lumbar vertebra. The placental shadow is subdivided into areas corresponding to the cotyledons which are demonstrated in this view. The umbilical artery is seen filled with dye and its entire course is well visualized. It is seen to pass into the uterus, and at the placental junction, it divides into its many ramifications which are clearly visible.

The placenta was examined after its delivery and was found to appear normal and to conform to the roentgenological appearances demonstrated on the placentogram. The patient made an uneventful postpartum recovery, and suffered no toxic or after effects from this examination.

We wish to stress that this is a preliminary report on a technique for examination of the placenta in utero. Further studies and correlation with pathological changes will be necessary before we can consider this an acceptable technique for general use.

SUMMARY

A brief review of the literature of the methods of roentgenological visualization of the placenta is presented. A new technique of placentography in the third stage of labor by use of diodrast injected into the umbilical artery is described. The roentgenological appearance of the placentogram obtained is presented. Subsequent studies with regard to pathology and improvement in technique are now being carried on.

University Hospital
Augusta, Georgia

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EOSINOPHILIC GRANULOMA OF BONES ASSOCIATED WITH INVOLVEMENT OF THE LUNGS AND DIAPHRAGM

By MAJOR ALFRED J. ACKERMAN, M.C.
Brooke General Hospital
FORT SAM HOUSTON, TEXAS

INVESTIGATIONS of recent years have brought about new concepts of the Hand-Schüller-Christian disease and its relation to reticulosis or non-lipid histiocytosis, and to the more recently described bone lesions, to which the term eosinophilic granuloma is generally applied. Most writers agree that the basic disorder in these diseases is a peculiar inflammatory histiocytosis. Transitions from eosinophilic granuloma into Letterer-Siwe's disease, on the one hand, and of Letterer-Siwe's disease into the classical forms of Hand-Schüller-Christian's disease, on the other, have been observed. Reports of cases in which the Hand-Schüller-Christian disease is associated with osseous changes characteristic of eosinophilic granuloma are—as far as we were able to ascertain—limited to the cases of Thoma, and Versiani and his collaborators. It may therefore not be amiss to report a case which we recently had the opportunity to observe. The findings in this case may be helpful in establishing the interrelation between eosinophilic granuloma and Hand-Schüller-Christian's disease on a firmer basis.

CASE REPORT

This patient, aged nineteen, entered an Army hospital in the fall of 1946 complaining of severe pain in the low back, radiating into both lower extremities, polydipsia, and polyuria. The patient was unable to stand or walk; he could move his legs in bed only slightly because of marked weakness.

The family history was not contributory. In childhood the patient had measles, mumps, chickenpox and whooping cough. He had always been rather sick and never felt very well. He has been suffering from backache since early childhood. This confined him to bed on numerous occasions, and necessitated the use of mechanical back supports. Even minor injuries incapacitated the patient over periods of months, and they were usually followed by pain radiating downward, along the distribution of the sciatic nerves, and by marked muscular weakness of the extremities. A roentgen examination in October, 1945, revealed destructive lesions in the lumbar spine, both iliac wings of the pelvis, and the femoral necks. These lesions were thought to represent multiple hemangiomata and were treated by irradiation. Following roentgen therapy, the patient's symptoms improved slightly. Shortly after induction into the service, in April, 1946, he noticed that he was drinking large quantities of water; the diuresis increased correspondingly, causing also frequent nocturia. The backache became much more severe, and the muscular weakness of the lower extremities made it impossible for the patient to stand or walk. He was admitted to the hospital, when one day he suddenly lost control of the lower extremities completely, and fell. In addition to these symptoms, there was also a slight hacking cough, which was apparently of a chronic nature. The patient lost approximately 15 pounds in weight in the last three months.

The patient was admitted to this hospital in October, 1946, and essentially the same clinical history was obtained.

Physical Examination. The patient was a well developed, well nourished young white male. The temperature was 98.6° F., pulse 90, respiration 24. Blood pressure 122/78. The positive findings elicited were: (1) fine moist rales at the base of the left lung posteriorly, (2) mild pain on deep pressure of all long bones of the body. Severe pain was elicited on pressure over the lower lumbar spine. Superficial and deep reflexes were normal but the patient could not move his legs fully even while lying in bed. The leg muscles were not atrophic, but rather flabby in character. (3) The foot muscles showed some atrophy, so that a pes cavus was present. (4) The finger nails were rather brittle.

Laboratory Findings. The urine showed a low

Fig. 1. Several calvarial defects in the parietal bones.

specific gravity varying between 1.004 and 1.006 on repeated examinations. The daily water intake and output measured from 3,500 to 8,000 cc., with an average during present hospitalization of approximately 5,000 cc. Two urine concentration tests showed a good concentration, evidenced by a fall in diuresis to 2,000 cc., and an increased specific gravity up to 1,024. The urine contained increased amounts of calcium; a quantitative test revealed 500 mg. of calcium in 5,000 cc. of urine excreted during twenty-four hours. The erythrocyte and leukocyte counts were normal; there was a slight eosinophilia (10 per cent). The blood calcium level was 10.3–12.0 mg. per 100 cc. The blood phosphorus was 4.4–5.8 mg. per 100 cc. The alkaline phosphatase showed 3.4 Bodansky units on one determination, and 6.9 Bodansky units on another examination. The acid phosphatase was 0.2 King-Armstrong unit. The total protein was 7.2 gm. per 100 cc., with an AG ratio 4.6/2.6. The blood cholesterol level was 185 mg. Corrected sedimentation rate was 10 mm. per one hour. Kahn test was negative.

Fig. 2. Large central bone destruction of the second cervical vertebra.

Fig. 3. Central defect in the fibula.

Roentgen examination of the skeleton showed several round areas of decreased density within both parietal bones, surrounded by a narrow sclerotic zone; the largest lesion measured approximately 1.5 cm. in diameter. There was a large area of bone destruction within the body of the second cervical vertebra. The ninth to eleventh right, and eighth and ninth left ribs showed oblong areas of rarefaction, which failed to produce pathological fractures, bone expansion, or periosteal reaction. The eleventh

and twelfth dorsal and all lumbar vertebrae were markedly altered. Normal trabecular bone architecture was replaced by "cystic" areas of rarefaction, involving the vertebral bodies and their processes. There was some lateral wedging of the vertebral bodies, whose articular surfaces were distinctly concave. Several "cystic" areas of rarefaction were observed in both iliac wings and both pubic bones. The long bones of the extremities were also involved. There were several small areas of rarefaction and one larger measuring 3 by 1.5 cm. within the medullary portion of the shaft of the right humerus. The endosteal surface of the cortex at the site of the larger lesion was eroded. Similar lesions were observed within both femoral necks, both distal femoral metaphyses and in the shaft of the left tibia and fibula. No expansion of bone or periosteal reaction was observed.

Fig. 4. "Cyst"-like rarefactions in the vertebrae and iliac wings.

An examination of the chest showed a moderate fibrosis of the dorsal segment of the left lower lobe, and a homogeneous density in the right lower lung field, obliterating the cardiophrenic sinus, and inseparable from the diaphragm. The oblique superior margin of this density was sharply defined. A combined diagnostic pneumothorax and pneumoperitoneum were performed. A good collapse of the right lung was obtained. Both diaphragmatic leaves were well outlined and the abdominal organs visualized. There was no evidence of atelectasis. The right diaphragm was approximately 2 cm. thick. The ventrodorsal films revealed a polycyclic soft tissue mass inseparable from the anteromedial portion of the diaphragm, extending slightly below the inferior margin of the diaphragm. In a lateral projection an oval

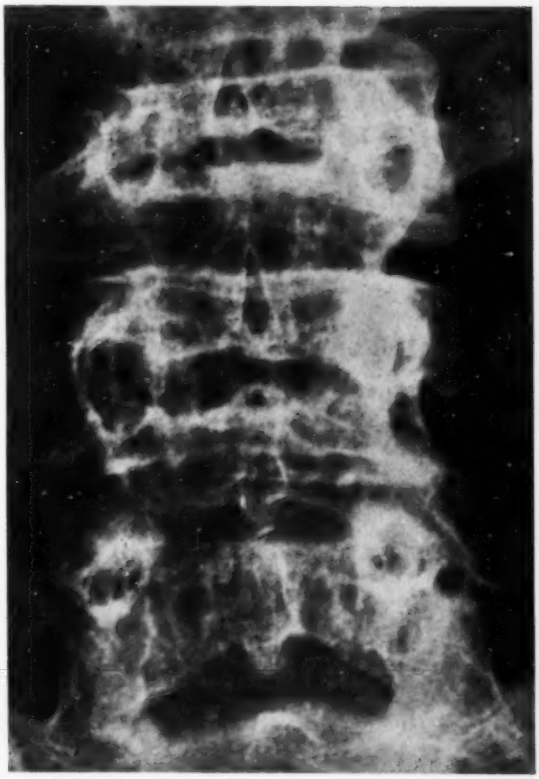

Fig. 5. Close up view of the third to the fifth lumbar vertebrae shows the significant bone changes.

shadow was demonstrated, obliterating the anterior sinus, and resting firmly on the diaphragm, from which it could not be separated. These findings were interpreted as consistent with involvement of the diaphragm, with extension of the mass into the anterior mediastinal space.

Fig. 6. Destructive lesions in the right pubic bone and the femoral neck.

FIG. 7. Destructive lesions in the left pubic bone and left femoral neck.

A section from an involved rib was obtained for biopsy. According to the description of the gross specimen, the cortex in the inferior costal groove contained a defect entering into the medullary cavity 13 by 3 mm. in size. The cortex was 1 mm. thick. Coarse bone traversed the medullary cavity, which was soft and reddish brown in color. The microscopic examination revealed sections of compact and cancellous bone. A few small fragments of soft tissue were present bearing the appearance of marrow. The fat cells were crowded out by a large number of eosinophils and a few macrophages showing some evidence of phagocytosis. Pathological diagnosis: Eosinophilic granuloma.

FIG. 8. Homogeneous density obliterating the right cardiophrenic sinus. Fibrosis of the left lower lobe.

DISCUSSION

Rowland defined Schüller-Christian's disease as a xanthomatous degeneration of the skeleton, characterized by proliferation

FIG. 9. Lateral view of the chest. The opacity on the right lies anterior to the mid-axillary line, and is inseparable from the diaphragm.

of fibrous tissue containing nests of xanthoma or foam cells, studded with birefringent esters of cholesterol. Many writers supported this view, which is still held by Thannhauser. This author classified Schüller-Christian's disease under "primary essential xanthomatosis of the normocholesteremic type." In this peculiar systemic disorder, foam cells develop singly or in large nests, despite the fact that the cho-

lesterol level of the circulating blood is normal. The reticulum cells and histiocytes retain normally the functional possibilities of embryonal cells, capable of forming various kinds of lipids and also of cholesterol. A disturbance of the intracellular enzymatic systems concerned with the formation of cholesterol may result in an accumulation of cholesterol within the cell, thus transforming it into a xanthoma cell.

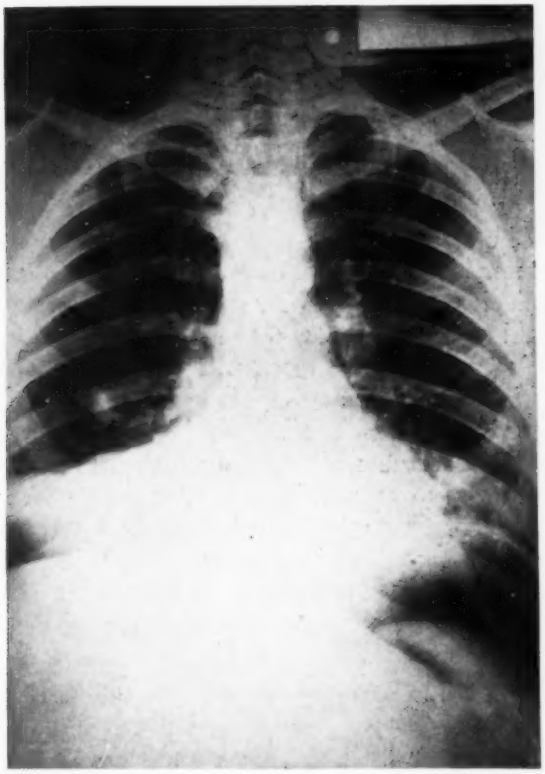

Fig. 10. Combined pneumothorax and pneumoperitoneum. The intrathoracic opacity is not due to atelectasis. The right diaphragm is much thicker than the left.

Not denying that granulomatous tissue is present to a greater or lesser degree in every xanthomatous lesion, Thannhauser found no justification in classification of the disease as "lipid granulomatosis." The inflammatory origin was suggested by Chester, who pointed out that proliferation of the reticulo-endothelial cells and histiocytes constitutes the chief pathologic alterations.

Fig. 11. Lateral view, demonstrating the circular opacities in the anterior sinus; they are intimately connected with the diaphragm and project below the inferior margin of the diaphragm.

Chester's observations have been confirmed by Letterer, Siwe, Wallgren, Farber, and others, who include aleukemic reticulosis, diffuse reticulo-endotheliosis and non-

Fig. 12. The liver is clearly separated from the diaphragm; the "tumors" at the right base are clearly demonstrated.

lipid histiocytosis in the same fundamental pathologic process. The variations in the clinical behavior and histopathologic appearance of the lesions, are, in Farber's opinion, due to the degree, stage of involvement, and localization of the same basic disorder, which, however, does not suggest a primary alteration of lipid metabolism.

Eosinophilic granuloma described independently by Otani and Ehrlich, and by Lichtenstein, and Jaffe, represents the latest number of this group. The close interrelations between this lesion and Letterer-Siwe's disease, and Schüller-Christian's disease were particularly emphasized by Farber and Green, and their views have been accepted by Mallory, Lichtenstein and Jaffe, and others. Mallory believes that the variations in clinical manifestations of the disease depend on the chronicity of the basic pathologic process. In infancy and early childhood, the clinical course is often acute, and the disease terminates fatally (Letterer-Siwe). The histiocytic lesions are widely disseminated in the soft tissues and the skeleton. In a chronic form (Schüller-Christian), observed in children or adults, the lesions may become collagenized, and lipidized. In addition to the skeletal manifestations, the disease affects not infrequently the pituitary gland, the brain, the lungs, and the heart. Eosinophilic granuloma, solitary or multiple, represents the mildest form of the disorder, and is confined solely to the skeletal system. This lesion responds well to surgical treatment or irradiation, and may heal occasionally by spontaneous resolution.

Insufficient evidence is available in the literature to prove that Hand-Schüller-Christian's disease can be associated with skeletal changes seen only in eosinophilic granuloma. Though it has been demonstrated that collagenization and lipidization in lipogranulomatous lesions have been engrafted on lesions which originally were dominated by histiocytes, still free of lipid, all 3 cases studied by Lichtenstein and Jaffe were in the lipogranulomatous stage at the time of examination. These authors, therefore, postulated that only those cases should be included in the group of Schüller-Christian's disease, which show, as the anatomic prerequisite, lesions classifiable as lipogranuloma. They did not deny, however, that it was logically probable that the bone lesions in Schüller-Christian's disease may originally resemble those of eosinophilic granuloma. The cases reported by Versiani and his collaborators, and by Thoma, in which eosinophilic granuloma of bone was associated with diabetes insipidus, may well present evidence to support this view, and perhaps make the rigid criteria proposed by Lichtenstein and Jaffe untenable. Our own case is an example, thus far, of rare association of eosinophilic granuloma with intrathoracic alterations. The evidence presented by these cases seems to be reasonable, since it is the association of Schüller-Christian's disease with this type of bone lesion which is in question. Apparently, the discrepancy between the histopathological appearance of osseous and visceral lesions has not been considered of paramount significance. It does seem worthy of emphasis that there are no reports of visceral lesions dominated by eosinophiles equivalent to those seen in the bones. It is interesting to note that the clinical history in our patient is of long duration, and the bone lesions are most likely of considerable standing. The prevalence of eosinophils in a bone lesion examined histopathologically does not appear to lend support to the opinions expressed by some authors, that only early lesions exhibit histopathologic features of eosinophilic granuloma and that the subsequent changes occur fairly rapidly. One may well raise the question whether or not there are considerable differences in the evolution of the basic pathologic process. It seems possible that the process can be arrested in a certain phase of evolution for a variable length of time and even become limited to it. In other cases, the eosinophils may appear only few in number and the histiocytes may represent the dominant cells. They, too, may exhibit variations in degree and rate of subsequent lipidization.

The clinical course and objective findings exhibited by our patient do not justify inclusion of this case in the category of Letterer-Siwe's disease. The significant alterations affect the bones and the lungs. There is no demonstrable evidence of involvement of other organs seen in Letterer-Siew's disease. A new, not previously reported, finding is the tumor of the diaphragm. This lesion was detected only after a combined pneumothorax and pneumoperitoneum had been performed. Prior to that, the paracardiac density in the right lower lung field was interpreted as an atelectasis of the lower lobe. The assumption that the diaghragm is affected by the same disease appears to be justified by the fact that muscle (heart) has been involved in other instances of the disease.

The classical craniohypophyseal manifestations of Hand-Schüller-Christian's disease are not always present. The exophthalmus is apparently caused by retroorbital proliferation of the granulomatous tissue. Diabetes insipidus could well be precipitated by involvement of the brain, dura, or both in the region of the hypophysis or the thalamus. Cases in which diabetes insipidus was observed without demonstrable calvarial defects militate against the opinion of Lichtenstein and Jaffe, that the presence of the craniohypophyseal manifestations depend solely on extensive involvement of the bones of the skull.

The literature on histiocytosis is expanding rapidly and the clinical and pathological observations thus recorded provide increasing evidence of the close relations between the variants of the disease. Association of Hand-Schüller-Christian's disease with osseous lesions identified as eosinophilic granuloma appears to have been demonstrated in at least several instances, including also the case presented here. The hypophyseal manifestations of the Schüller-Christian triad can apparently occur without extensive skeletal involvement of the skull. Involvement of the diaphragm has not, as far as we know, been reported in the past, but obviously represents another site of muscular involvement.

Many aspects of this general disorder remain vague, and need further clarification. It does not appear clear to us why an inflammatory process in its most florid form occurs only in young children. We do not understand why the visceral lesions of this disorder fail to exhibit histopathological changes equivalent to "eosinophilic granuloma" of bone, although the discrepancy between the histopathological characteristics of the visceral and osseous lesions does not seem to be significant to the pathologists. We are not certain that the "eosinophilic" phase of the bone lesions is significantly related to the age of these lesions. Certainly the fact that the other phases have been observed more frequently does not preclude the possibility that the eosinophilic phase may persist longer than several weeks or months. The history in our case points to a long duration of the bony changes, which were definitely demonstrated over one year ago.

It does seem possible that there are significant variations in the evolution of the basic pathologic process, and that the clinical manifestations of the disease in its chronic forms depend largely on the localization of the lesions. We also doubt that the acuteness of the disease in a given case can be determined from the histopathological appearance of any single lesion. The prognosis depends most likely on the clinical course of the disease.

Granting that the evolutional variations of the anatomic life cycle of the disease are inferred, it may be rightly pointed out that the pathological concept of the disease has undergone considerable modification since the appearance of the first reports on eosinophilic granuloma alone. Further observations may prove the present definition of the disease not less inadequate.

CONCLUSIONS

1. A case of multiple bone lesions, associated with involvement of the lungs and diaphragm, is presented.

2. Histopathological study of an affected rib revealed changes characteristic of an eosinophilic granuloma.

3. The histopathological evidence tends to confirm the current views that there is a close relation between eosinophilic granuloma and Hand-Schüller-Christian's disease. The postulation that only cases with lesions classifiable as lipogranuloma to be included in the group of Hand-Schüller-Christian's disease appears too rigid. This case demonstrated the association of eosinophilic granuloma with pulmonary and diaphragmatic involvement, whereas the cases reported by Versiani and his collaborators and Thoma emphasized the coexistence of eosinophilic granuloma and the craniohypophyseal manifestations of the disease.

4. It is worthy of further study to observe whether or not the eosinophilic granuloma is only an early manifestation of the basic disorder and is soon replaced by other elements of the evolutional cycle. It may well be that the histological characteristics of the lesions are retained for considerably longer periods of time than heretofore assumed.

5. It does not seem warranted to assume from an examination of one bone lesion that all other lesions present the same histopathological structure.

6. The involvement of the diaphragm is apparently an observation not recorded in the literature previously. It obviously represents another example of a muscular organ which can be involved in this disease.

7. The method of combined diagnostic pneumothorax and pneumoperitoneum again proved of definite value in establishing the anatomical relations of homogeneous densities, inseparable from the diaphragm.

Brooke General Hospital
Fort Sam Houston, Texas

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Vol. 58, No. 6

RADIOACTIVE SODIUM AS A TOOL IN MEDICAL RESEARCH*

By EDITH H. QUIMBY, Sc.D.
College of Physicians and Surgeons
NEW YORK, NEW YORK

THE production of radioactive sodium was announced in 1934, as the result of bombarding sodium with neutrons, by Fermi and his collaborators, and later by the Curie-Joliots.[1,2] In the same year, Lawrence produced it by deuteron bombardment in the cyclotron.[3] It was the first artificially radioactive substance found which had a half life of more than a few minutes; its half period of about fifteen hours, and the fact that it emitted penetrating beta and gamma rays led to some over-enthusiastic prophecies that it would soon displace radium in medicine. This has not been the case, but it has been found very useful in its own right.

Radioactive sodium can be produced in five different ways, by bombarding sodium with neutrons or deuterons, magnesium with neutrons or deuterons, or aluminum with neutrons. In every case the product is the same, a sodium nucleus containing an extra neutron and therefore having atomic weight 24 instead of 23. The various reactions are shown in Table 1. In every case the radioactive atoms disintegrate by the same stages—ejection of a beta ray, transforming the nucleus to magnesium, and emission of gamma rays as the magnesium becomes stabilized (Fig. 1). This disintegration proceeds at such a rate that half the radioactive atoms are destroyed in 14.8 hours, half the remainder in a like period, and so on.

In practice, most of the radioactive sodium used up to the present time has been made in cyclotrons, by deuteron bombardment; now it is also to be made available from the uranium "pile" at Oak Ridge. The sodium in the bombarded target may be in the metallic state or may be a salt. In either case, after removal from the cyclotron or pile, the sodium is chemically separated from other substances, if necessary, and is usually delivered for use in the form of a solution of sodium chloride. In this solution only an extremely small fraction of the sodium atoms are radioactive; the remainder is in the ordinary stable form.

TABLE I

$$Na_{11}^{23} + +n_0^1 = Na_{11}^{24}$$

$$Na_{11}^{23} + H_1^2 = Na_{11}^{24} + H_1^1$$

$$Mg_{12}^{24} + n_0^1 = Na_{11}^{24} + H_1^1$$

$$Mg_{12}^{26} + H_1^2 = Na_{11}^{24} + He^4$$

$$Al_{13}^{26} + n_0^1 = Na_{11}^{24} + He_2^3$$

In living animals, sodium is uniformly distributed throughout extracellular body fluids, the sodium ion passing freely back and forth across capillary membrane. When radioactive sodium is administered by mouth or intravenously, it rapidly appears throughout the body. Since it emits penetrating radiation, its presence in a part of the body can be demonstrated by bringing near it a sensitive detector of radiation. The instrument usually employed is a Geiger-Müller counter, which can detect the ionization due to a single atomic disintegration. Counting tubes can be of different sizes, and shielded to admit radiation from only a definite region. Figure 2 shows some which have been useful in work with radioactive sodium.

Soon after the discovery of radiosodium, experiments were made to see how promptly the material, orally or intravenously administered, could be demonstrated in an extremity.[4] Studies of rate of excretion and

* Presented at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

deposition in various organs and tissues followed.[5] These may be characterized as typical tracer studies, rather than as uses of radioactive sodium as a tool.

One of the first applications which might be characterized in this manner was the work of Kaltreiter and his associates at the University of Rochester in the determination of the volume of the extracellular fluid of the body.[6] Previous measurements of this sort had been done with sucrose, sulgans, and therefore the volume determined by this substance includes some intracellular fluid. Sodium is excreted very slowly and it does not enter blood or tissue cells appreciably, but it does slowly enter bone. However, determinations made with it within three to six hours after administration should be quite satisfactory. The use of radiosodium has the advantage of ease and simplicity, if the material and Geiger counter are available. Kaltreiter and his

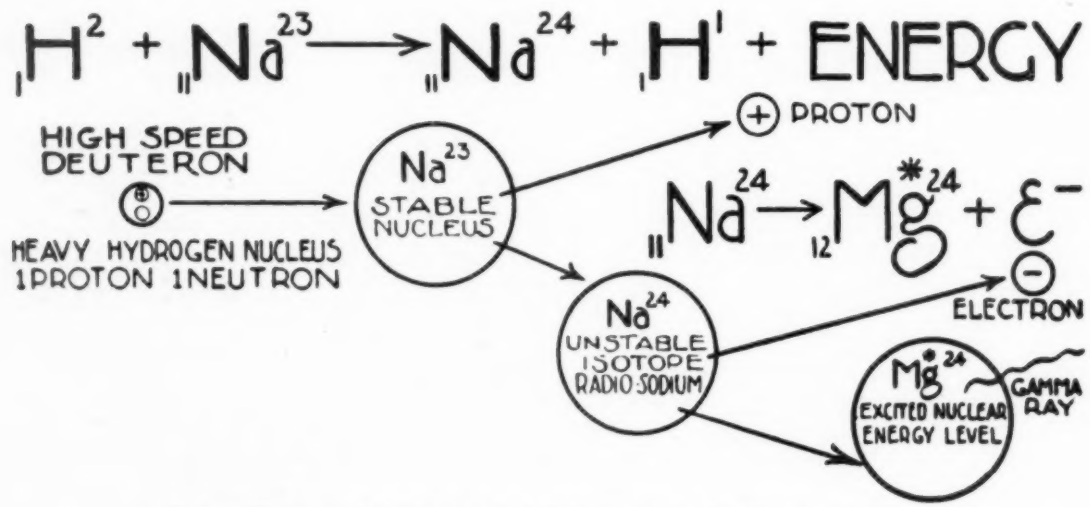

FIG. 1. Diagram of production and disintegration of radioactive sodium.

fate, and thiocynate, but all of these have definite drawbacks. The principle is simple. Some hours after the intravenous administration of the test chemical, a sample of blood plasma is obtained and the concentration of the substance measured in it. Up to this time, all material excreted has been saved, and the amount of the test substance lost in this manner determined. Assuming that the material is uniformly distributed in extracellular fluid, the amount remaining in the body (the amount administered minus the amount excreted) divided by the amount per unit volume in the serum, gives the volume of fluid in which it is dissolved. Sucrose and sulfate are not very satisfactory because of the speed of their excretion. Thiocyanate is slowly excreted, but it enters the red blood cells and the cells of certain glandular or-

group, and others, have made series of measurements in both normal and diseased subjects, using radioactive sodium and thiocyanate simultaneously. Results obtained with sodium, corrected for absorption in bone, give about 21 per cent of body weight as "sodium space" extracellular fluid, of which 15 per cent is plasma and 85 per cent interstitial fluid. Corrected results with thiocyanate give a "thiocyanate space" representing 23.5 per cent of body weight. Repeated determinations on the same individual check well, provided general health is maintained. In patients with a disease producing serous effusion, concentration of radiosodium in pleural and ascitic fluid is essentially the same as in blood serum. In such patients the volume of extra fluid would be included in the extracellular volume determined by the use of

radioactive sodium, and hence an estimate of the volume of excess fluid could be made by comparing the result with the normal for an individual of essentially the same weight. Especially advantageous in such a problem would be repeated measurements in the same subject.

Leading directly from this work is the study of Fox and Keston at Columbia University on the mechanism of shock from burns and trauma, as traced by radioactive sodium.[7] Various clinical studies had indicated that in shock caused by extensive burns a redistribution of sodium and potassium took place. It appeared that the "antisodium barrier" between extracellular and intracellular fluids might have broken down. This could be tested with radioactive sodium by determining "sodium space" as just described. If this space is very much larger than normal, and there has been no commensurate increase in body fluid, as indicated by edema, it is evidence that the sodium is infiltrating into tissues where it does not normally go. In animal experiments, where shock was produced by a standard procedure, and analyses made with radiosodium, it was found that the burned tissues (skin and muscle, which normally contain very little sodium) did indeed take up a large proportion of the administered isotope. The consequence of this concentration in the damaged region would be a depletion of this electrolyte from normal parts of the body. If this is true, administration of an excess of isotonic sodium salt to the animal in shock should be remedial, and this in fact was the case. Burned animals treated by intraperitoneal injection of normal saline equal to 16 per cent of their body weight recovered, while similarly burned ones left untreated invariably died. In humans with severe burns the increase in "sodium space" together with the disappearance of sodium from the urine, indicated that the sodium

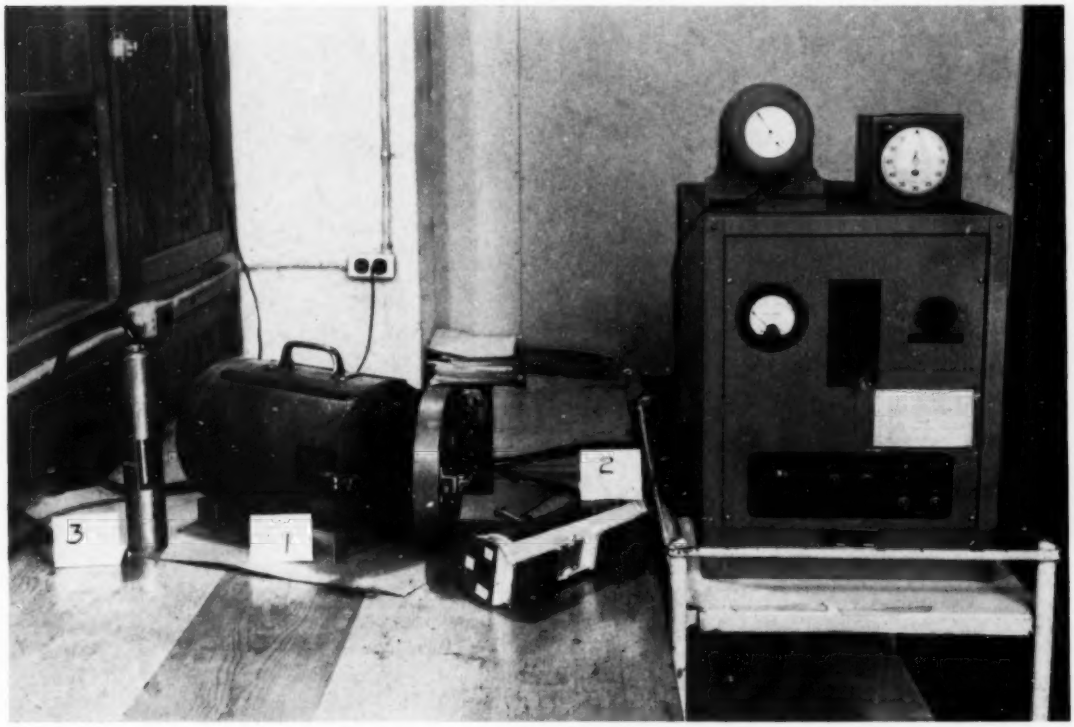

Fig. 2. Geiger Counter: scaling circuit and counting tubes.

was being withdrawn from normal equilibrium in extracellular fluid. In one case it was possible to demonstrate with a Geiger counter that the radioactive sodium deposited within a burned region was considerably greater than in the corresponding part of the uninjured limb.[8] Successful treatment in this case and in similar ones was carried out by the administration of large volumes of isotonic (sixth molar) sodium lactate solution by mouth or infusion. It appears that replacing the withdrawn sodium together with extra water aids in re-establishing fluid balances, maintaining blood volume and blood pressure, and thus combatting shock. In a preliminary series of cases, results by this type of treatment were as satisfactory as with intravenous plasma, and of course the procedures are much simpler. A more complete report on a larger series of cases is promised but has not yet appeared.

A somewhat similar study is one concerned with mode and rate of formation of cerebrospinal fluid, by Greenberg and his associates at the University of California Medical School.[9] The key to the problem has been stated to be the role played by the tissue membranes separating the blood plasma and cerebrospinal fluid, in the distribution of ions and molecules between these two fluids. Questions are whether elements of the barrier membrane perform an active secretory function, whether the distribution of substances between the fluid and plasma is controlled only by passive diffusion, or whether these substances pass from plasma into extracellular fluid of brain and spinal cord and from these into spinal fluid. In the last case equilibrium would not be between plasma and spinal fluid, but between the latter and the extracellular fluid of the central nervous system.

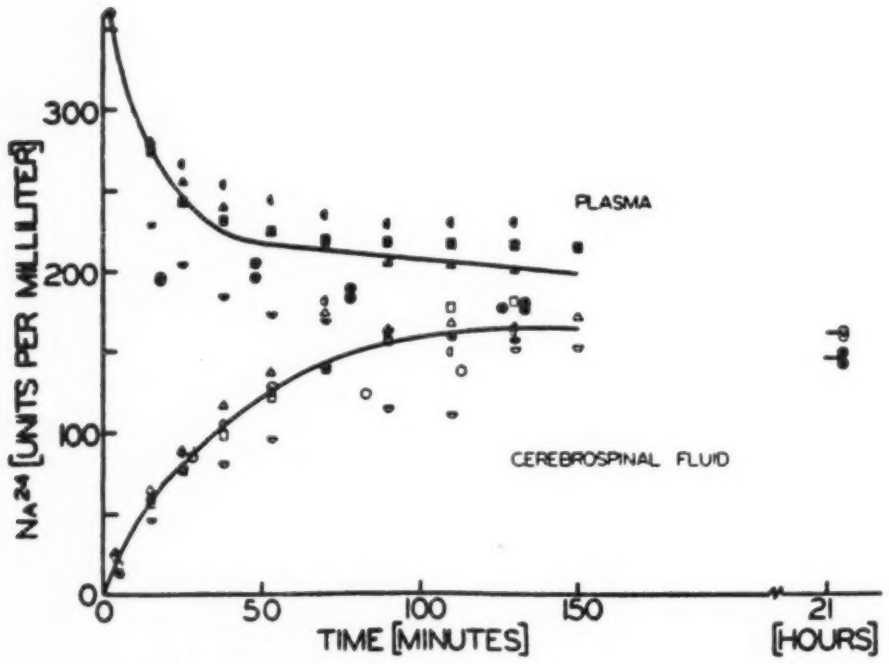

Fig. 3. Curves showing rate of disappearance of radioactive sodium from blood plasma and of its appearance in freshly formed cerebrospinal fluid in normal untreated dogs. Each experiment on an animal is represented by a characteristic symbol which is solid for plasma values and open for spinal fluid. Note change in time scale (indicated by break in abscissa) and fact that ultimately concentration is greater in spinal fluid than in plasma. (Courtesy of Dr. David M. Greenberg.)

The study was undertaken by injecting various radioactive substances intravenously and determining their rate of appearance in the spinal fluid. Large dogs were used as subjects; after sodium pentobarbital anesthetization a cisternal puncture was done and all pre-formed cerebrospinal fluid withdrawn. Continuous drainage was maintained to collect the newly formed fluid. The radioactive material was then injected and its rate of appearance in the newly formed fluid obtained. Radioactive sodium attains equilibrium in extravascular fluid in these dogs in about an hour. It begins to appear in the spinal fluid within a few minutes but does not reach plasma level for many hours. After twenty-one hours it is about 10 per cent higher in spinal fluid than in plasma, as would be expected on the basis of their respective chemical compositions. Sodium curves of these authors are shown in Figure 3; similar curves were obtained for other radio-isotopes, but the rates were different. Some elements showed a maximum in the cerebrospinal fluid, others did not. For all elements used, the ratio of concentration in spinal fluid to that in plasma took many hours to reach the values found in the stable state by chemical analysis. The delay was selective and varied greatly for different ions. The authors conclude that the hindrance to the free passage of ions from the blood stream to the extracellular fluid of the central nervous system, and the deviation from the Donnan law of distribution of the steady ratios of the concentrations of these ions between the spinal fluid and the plasma, constitute evidence that the exchange between the blood and the brain takes place by a process of secretion and not by simple diffusion or ultrafiltration.

Experiments of the same general type were carried out by Visscher and his coworkers at the University of Minnesota to investigate movement of water and ions between intestinal lumen and blood,[10] and by others to study transfer of ions across membranes in different body regions.

Radioactive sodium was used by Hubbard, Preston, and Ross to determine the velocity of blood flow in infants and young children. The material was injected into one antecubital vein and the time of its arrival at the opposite hand determined by a Geiger counter.[11] Their series was small and the results quite variable, but were at least as satisfactory as those obtained by other methods.

This use of the material would readily suggest itself to anyone concerned with circulation times, and similar studies were initiated independently by Smith and Quimby in connection with work on patients suffering from peripheral vascular disease.[12] The material was injected into an antecubital vein, with the window of the portable shielded Geiger counter (*2*, Fig. 2) against the sole of the foot, and arm-to-foot circulation times measured. After a small group had been tested, it seemed that no valuable correlations between clinical condition and circulation time would be established. However, the work led to the development of a test which has proved very useful.

As equilibrium of radiosodium concentration is built up between plasma and extracellular fluid, the counting rate of the Geiger counter at the foot increases, because the blood continues to bring sodium to the capillaries, where some of it diffuses out into the interstitial fluid and remains there. A curve can be plotted showing increase in counting rate with time after administration of the material, and it has been found that the shape of this curve can often be correlated with clinical condition. In individuals with no known vascular disturbance the "build-up curves," calculated on the basis of 100 microcuries of radiosodium administered, all fall within the relatively narrow region indicated in Figure 4 as "Normal Range." For patients with various vascular disorders, the curves may be within, above, or below this region. A very low curve may be due to arterial obstruction, arteriosclerosis, hypertension, spasm, degeneration of capillaries, or com-

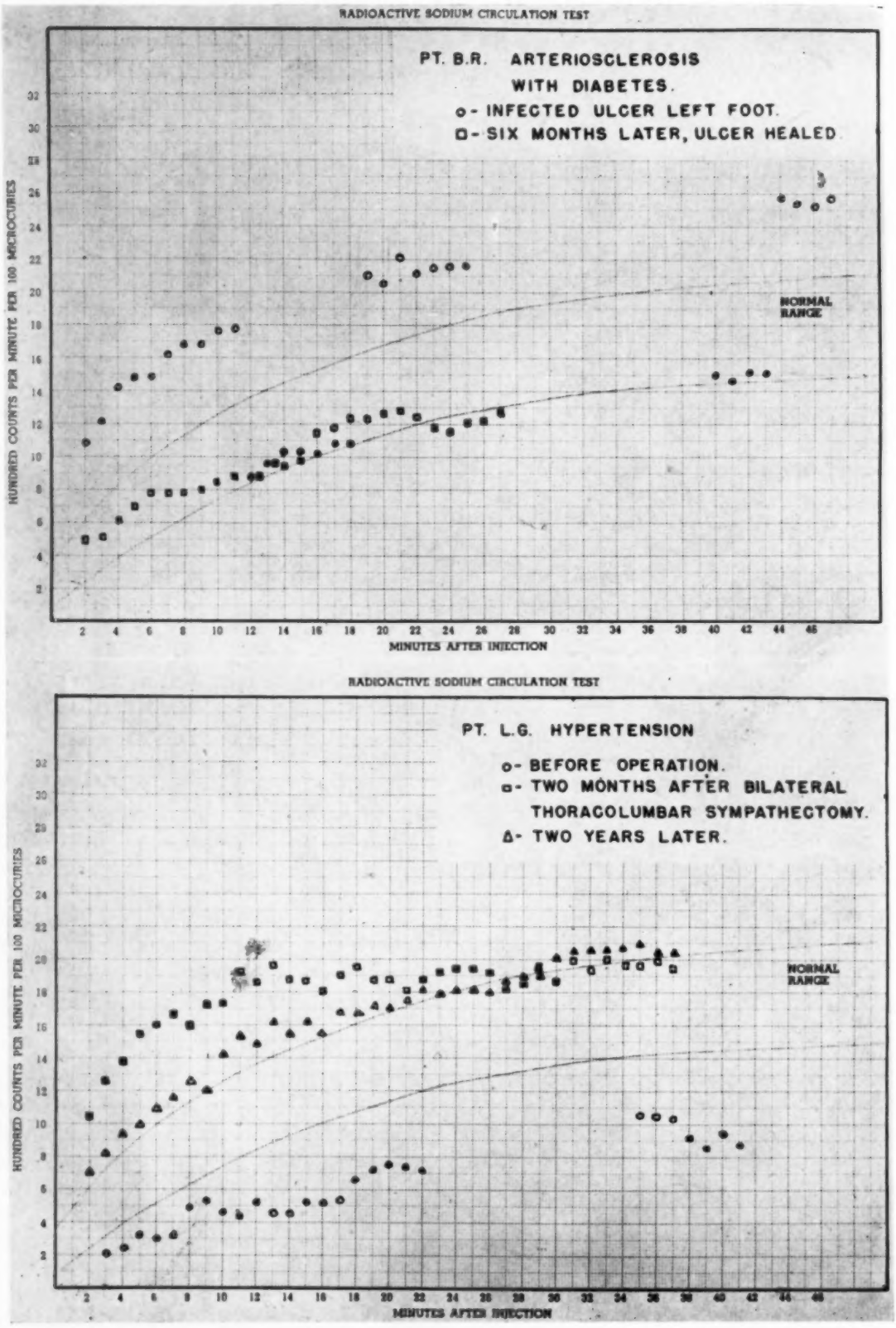

FIG. 4. Radioactive sodium "build-up" curves in a patient with arteriosclerosis and an infected diabetic ulcer, healed by local treatments, and in a patient with severe hypertension relieved by thoracolumbar sympathectomy. For details see text.

binations of these factors (or others). A very high one is due either to inflammation (increased blood supply) or to relaxation of vessel walls by nerve block, sympathectomy, or other reason. Numerous illustrative curves have been published; some typical ones are shown in Figure 4. In all these curves, solid symbols represent counts made against the right foot, open ones against the left. The lower chart shows data for a forty-year-old man with severe hypertension, relieved by bilateral thoracolumbar sympathectomy. The lowest curve (points indicated by circles) represents a test made before the operation. At this time the patient was unable to work and subject to very severe headaches. The two upper curves (squares and triangles) are for tests made two months and two years respectively after the operation. The patient's blood pressure is still rather high but he is symptom-free, and working at an active occupation. Other hypertensives with very low preoperative curves have responded to the operation in a similar manner. On the other hand, those with original curves in or near the normal range are not likely to show a high curve after sympathectomy, and they usually obtain little or no relief from the operation. The explanation appears to be that the very low curve is due, at least partly, to spasm, which is released by the operation. On this basis, it is sometimes possible to foretell whether this operation should be beneficial in a particular case.

In the upper chart the top curve (circles) indicate the original condition in a diabetic arteriosclerotic with an infected ulcer in the sole of the left foot. In view of the apparent good blood supply to the affected foot, conservative therapy was decided upon. The squares show the condition eight months later, when the infection had been healed for five months; both feet were then normal and have continued so. In many such cases it has been possible to avoid amputation by assuring the surgeon of the presence of good blood supply. In cases of gangrene where the initial curve is low and the blood supply at the foot evidently poor, so that surgery is indicated it has been possible to determine a level below the knee at which adequate blood supply existed, and at which amputation could safely be performed. This has lessened the number of above-the-knee amputations.

Such radiosodium "build-up curves" have been useful aids to the medical staff in diagnosis, prognosis, and the selection of therapy in arteriosclerosis, hypertension, thromboangiitis obliterans, Raynaud's disease, various thrombi and emboli, trench- and immersion-foot, frostbite, and other conditions. Repeated tests on the same individual give information regarding the course of the disease and the efficacy of various therapeutic measures. A study is under way at the present time to test the values of various drugs and physical therapy procedures in a selected group of patients with peripheral vascular disease.

In early work with a certain type of drug therapy, it was found desirable to cut off circulation from the extremities for a few minutes after injection of the material. For this purpose, blood pressure cuffs were applied close to the trunk and inflated to 250 mm. of mercury pressure. In order to determine the efficiency of such a tourniquet, in different types of individuals, radioactive sodium "build-up" studies were made by Quimby and Karnofsky similar to those already described as being used in vascular diseases.[13] A tourniquet was applied to one leg in the usual manner, the other being left free. Radiosodium was injected into an arm, with the counter at the feet. As would be expected, the build-up in the unblocked foot followed the normal pattern already established. In the foot with circulation checked by the tourniquet, various degrees of retardation were found, depending on the obesity of the individual and the amount of pressure applied. Figure 5 shows curves for a very obese individual and a tall rather thin one. Solid points are for the blocked foot, open ones for the unblocked one; the circles are for the thin patient and the squares for the stout one.

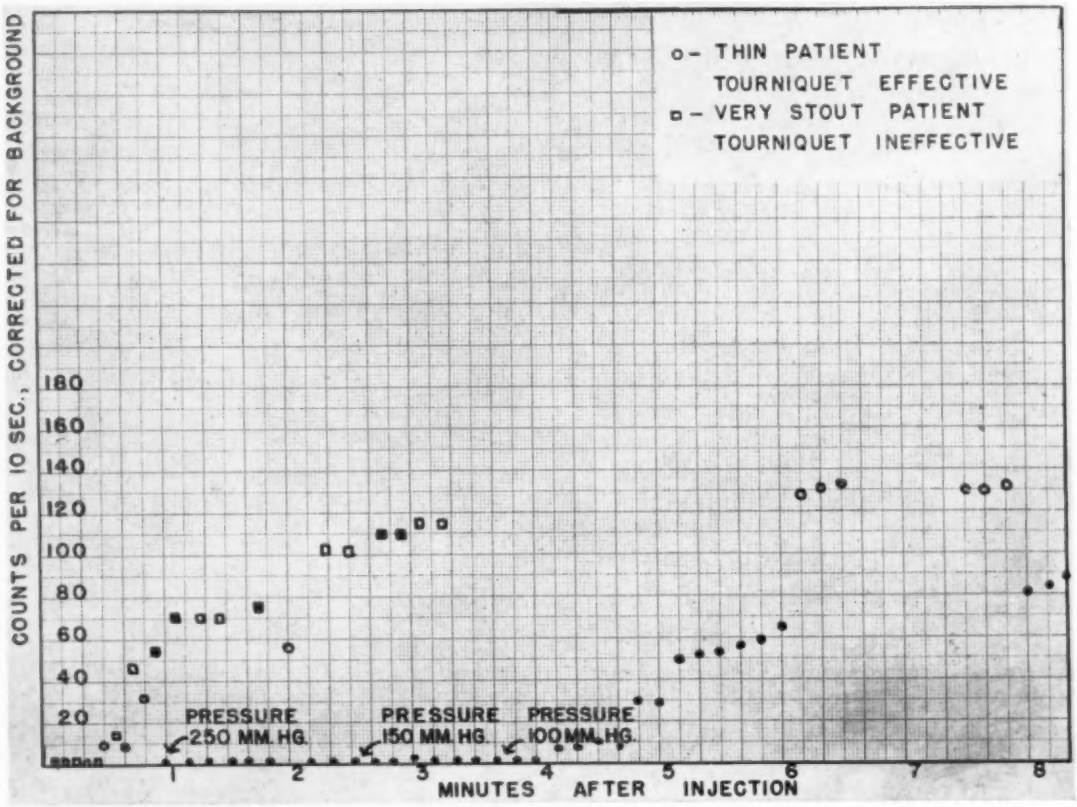

Fig. 5. Radioactive sodium "build-up" curves in patients with tourniquets applied to the upper thigh. Closed symbol, blocked foot; open symbol, unblocked foot.

In the latter, no blood reached the foot until the pressure had been reduced to something between the systolic and diastolic; it then came rapidly. For the stout patient, it was evident that a better type of pressure cuff must be devised.

In an investigation of mechanical methods of artificial respiration, it was desired to know whether blood could be made to circulate by a mechanical respirator if coagulation had not occurred. Pulmonary ventilation alone is not sufficient to produce resuscitation, particularly if the circulation has stopped. Oxygenated blood in the lungs is of no value unless it can be moved out and transported to the vital centers of the nervous system. The question can be answered by the introduction of a tracer substance into the vascular system of an animal immediately following its death by asphyxiation, and recording any movement of this substance during the application of the resuscitative procedure. Such an investigation was carried out by Thompson, Quimby, and Smith, using radioactive sodium as the tracer.[14] Dogs were anesthetized and an intravenous injection of heparin administered to prevent clotting of the blood. An endotracheal tube with occlusion cuff was inserted and clamped off, and the animal allowed to succumb to obstructive asphyxia. About half an hour after clinical evidence of death, a small quantity of radioactive sodium was injected into a femoral artery or vein (separate studies were made for the two), the counter placed over the carotid-jugular region, and the resuscitator started. After a period of artificial respiration which varied with the type of apparatus used, radioactive sodium arrived in the vessels under the counter, and continued to increase in amount there

as long as the count was followed—from thirty minutes to an hour. In animals with no respirator, or with no heparin, the material was never demonstrated above the diaphragm. It was thus proved that the resuscitative procedures did circulate the blood, and that passive diffusion played no significant part. Figure 6 shows curves for four of the animals, with three different respirators and with none. At the end of the resuscitative efforts, the animal was autopsied and blood taken from various regions was tested for the presence of the radioactive isotope. If was found in both chambers of the heart and in large veins and arteries throughout the body, but not in uniform concentrations. In the living animal, within less than a minute after injection the sodium content of the blood taken from any of the larger vessels is the same, due to the complete mixing after a few passages through the heart. It has been concluded from this work with dogs that when artificial respiration is employed in asphyxia, the administration of heparin to prevent clotting should increase the possible recovery time of the patient by making it possible to move oxygenated blood even after the heart has stopped beating, although the movement will be slow and the oxygen content not uniform.

Penicillin in an aerosol administered by means of a nebulizer has been found useful in some cases of lung abscess, certain bronchial infections, asthma, etc. In the investigation of a number of problems concerned with its administration, it appeared that radioactive sodium might be an aid, since the vehicle for the pencillin is normal saline. Questions to which answers were sought were:

a. Does the penicillin actually reach the

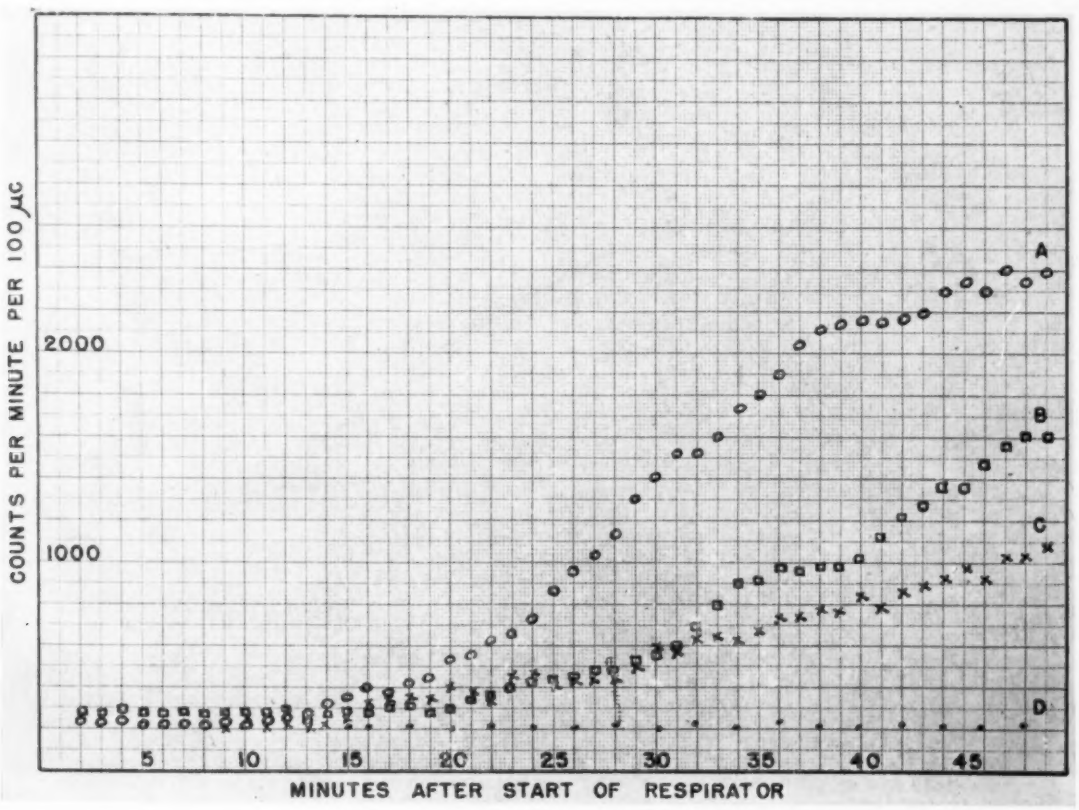

Fig. 6. Radiosodium "build-up" curves demonstrating movement of blood by artificial respiration in dead but heparinized dogs. *A*, respirator using alternate pressure and suction; *B*, suction alone; *C*, pressure alone; *D*, no respirator.

outermost alveoli, or is it mainly deposited in the larger bronchi?

b. Does the dose in the alveoli continue to be built up with prolonged inhalation, or is an equilibrium reached after a short time?

c. Can it be determined whether one type of nebulizer is more efficient than another?

d. Can the efficacy of the addition of various substances to the aerosol, to change particle size, be tested?

e. Can optimum conditions of temperature and humidity for the aerosol be established?

Determinations of penicillin blood levels have failed to furnish satisfactory answers to these questions. Talbot, Quimby, and Barach have obtained some information with radiosodium, of which a part is ready for publication.[15] Other studies are planned.

Radiosodium concentrations have not yet been shown to correspond exactly to penicillin concentrations in the aerosol, but for the preliminary tests it has been assumed that this is the case. Of course the sodium will not remain where it is delivered by the vapor, but will promptly pass through the lung cell walls, enter the blood stream, and be distributed throughout the body. Even so, a considerable amount of information can be gained from measurements made immediately after its administration.

As the tests were set up, the subject started with a known amount of radioactive sodium in the nebulizer, and all exhaled air passed through a train of traps, condensers, and precipitators. At the end of the test, the nebulizer and all parts of the exhaled air train were thoroughly washed and the radioactive isotope content in the washings measured. It could be assumed that the subject retained whatever was not

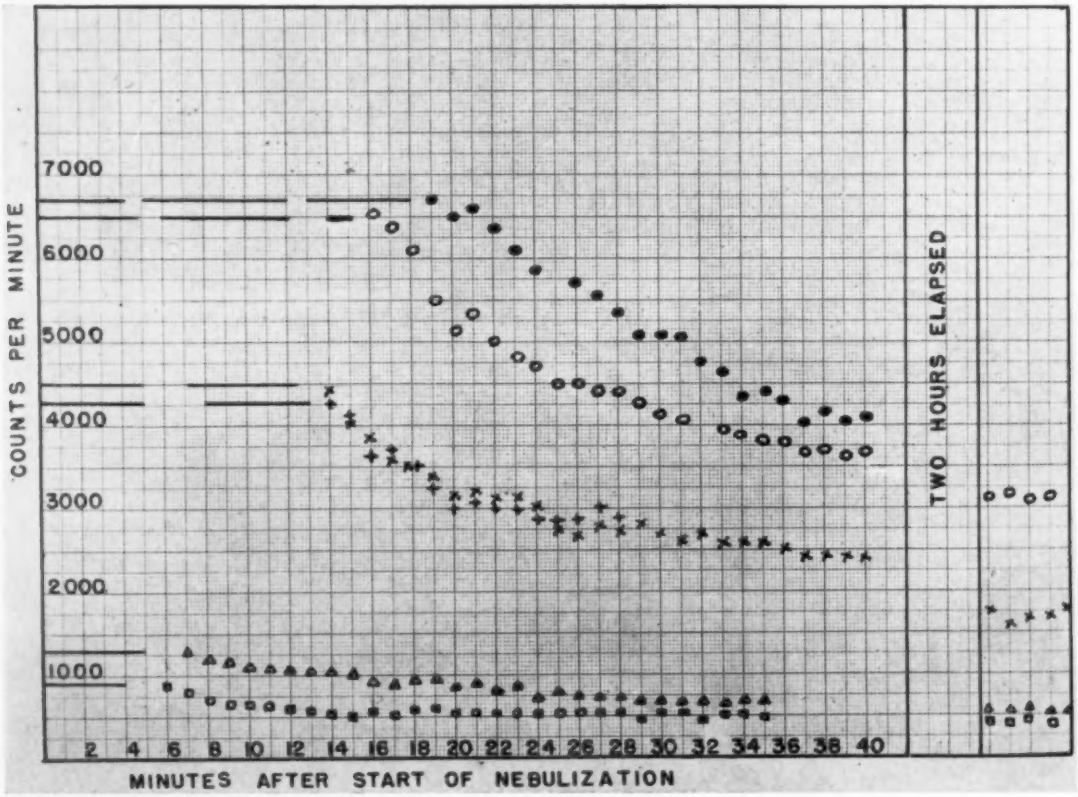

Fig. 7. Curves showing delivery of radioactive sodium to axillary region by inhalation of nebulized normal saline, with subsequent removal of the sodium into the blood stream. For details see text.

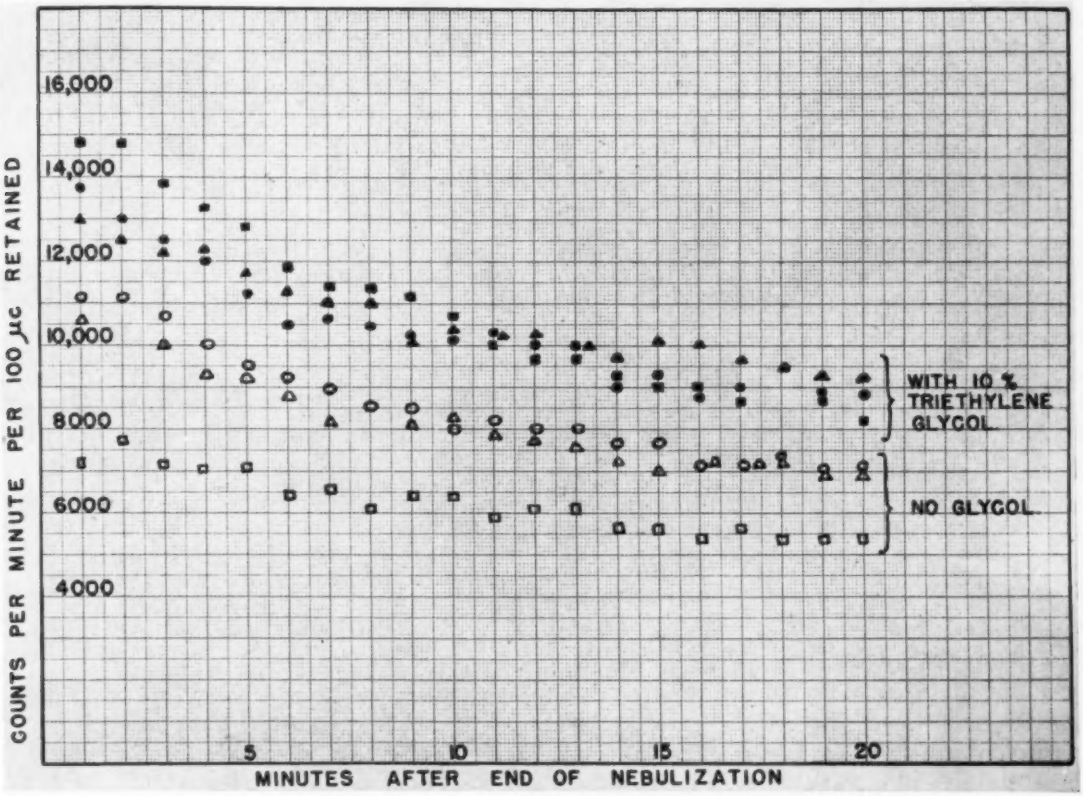

Fig. 8. Curves showing increase of delivery of radioactive sodium to axillary region by addition of 10 per cent triethylene glycol to the saline.

thus accounted for. (It was further possible to make later measurements on the radioactivity of the entire individual and estimate how much sodium he had retained, by comparison with individuals who had swallowed a known amount.) After the subject had inhaled for a predetermined time, he was quickly taken to a room some little distance away, to the Geiger counter. The same shielded counter was used as in the work on vascular disease; it could be placed over different regions and counts obtained. The questions listed above were answered as follows:

a. After a breathing period, counts were taken over the upper esophagus, the sternum, and the lateral lung, high under the axilla. They were essentially the same in all three positions. It appeared that material was definitely being delivered at the outer part of the lung. However the question was raised that, since sodium gamma rays are so penetrating, it might be possible that readings obtained at the axilla were actually due to material near the center of the body. Accordingly other subjects swallowed amounts of the isotope equal to those retained by the inhalers. In such cases the count at the axilla was less than one-third of the count after nebulization. Evidently a considerable part of the count is due to material far out in the lung.

b. Individuals inhaled for different times, material being added to the nebulizer every five minutes, so that the volume there available did not change greatly. Figure 7 shows levels attained by three pairs of individuals breathing about five, ten, and fifteen minutes, against the same concentration of material. The solid line in each case starts at the beginning of inhalation, breaks indicate pauses for adjustment or refilling the nebulizer. The rapid fall of the curves indicate the departure of

sodium from the lungs. Equilibrium appears to be attained fairly promptly however, for the counts at two hours are only slightly lower than those for one-half hour.

c. Three different nebulizers tested with the same individuals showed no appreciable differences. However the mechanical differences among these were not marked; it is probable that greater variations would result in different uptakes of sodium.

d. The addition to the solution of 0.2 cc. of 5 per cent triethylene glycol made no difference in sodium uptake, but when the same amount of 10 per cent glycol was used, the count in every case was higher than for the plain saline (Fig. 8).

e. When a rebreathing system was used, if the balloon for rebreathed air was kept immersed in hot water, thus assuring warmth and humidity in the inhaled material, the count was always higher than for the same individual when the rebreathed air was cold.

Much work remains to be done on this problem; the data here presented merely indicate the possibilities.

In all such experiments as the ones described, using radioactive tracers, it must be assured that the accompanying amount of radiation is so small as not to constitute a danger to the subject, and not to influence the experimental findings. Marinelli has published a method whereby the radiation dose can be estimated for material administered and remaining within the body until its complete decay.[16] On this basis, 1 microcurie of radioactive sodium per kilogram of body weight delivers a whole body radiation of about 0.11 r over an effective period of about two days, when both the beta and gamma rays are considered to be entirely absorbed within the body. The accepted tolerance dose for continuous irradiation is 0.1 r daily[17] hence it is safe to use tracer doses of 2 or 3 microcuries of radioactive sodium per kilogram of body weight, and to repeat them a few times at reasonable intervals. *This dosage does not apply to any other radioactive isotope.* In most of the work described herein, doses have been of the order of 100 microcuries, which is usually less than 2 microcuries per kilogram.

The foregoing paper presents a condensed account of some uses of a single radioactive element, sodium 24, as a tool in experimental medicine. The information is collected partly from the literature and partly from personal experience. It is not suggested that this covers the entire field of work with sodium; there is doubtless much more, both published and unpublished. As radio-isotopes become more readily available, and their measurement somewhat simplified, it is to be expected that work of this type will often become standard experimental procedure.*

630 West 168th St.
New York 32, N. Y.

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TISSUE DOSAGE IN RADIO-ISOTOPE THERAPY*

By ROBLEY D. EVANS
Massachusetts Institute of Technology
CAMBRIDGE, MASSACHUSETTS

THE biological action of roentgen rays is, of course, due to the effects on living cells of high-speed secondary electrons produced by the primary roentgen rays. The beta rays from a radioactive isotope are also high speed electrons. These beta rays can therefore be expected to produce tissue effects similar to those produced by roentgen rays. The beta rays have a maximum range of only a few millimeters of tissue. Therefore, the beta radiation doses are usually confined almost exclusively to the tissue actually containing the radioactive isotope, and the dosage rate at any time is proportional to the concentration of the isotope in the tissue.

It might be desirable to express the radiation doses produced by the beta rays in some fundamental energy units, such as ergs per gram of tissue. Ordinarily, however, the doses are converted into equivalent roentgens, with air as the standard substance. A number of authors have discussed special and general cases of the estimation of beta ray doses from radioactive isotopes.[1,2,3,4,5,6,7,8,9,10]

One roentgen of roentgen rays, by definition, produces 1 electrostatic unit, or $1/4.80 \times 10^{-10} = 2.08 \times 10^{9}$ ion pairs, per cc. (0.001293 gm.) of air, or 1.61×10^{12} ion pairs per gram of air. An average of 32.5 electron volts (e.v.) is expended[11] to form each ion pair in air, therefore the roentgen corresponds to the absorption of 5.24×10^{13} e.v. of energy (which is about 83 ergs) per gram of air. An amount of beta radiation which delivers 5.24×10^{13} e.v. per gram of air will deliver approximately this same amount of energy per gram of tissue, and may be called one roentgen-equivalent-physical (rep.). Thus:[12]

$$1 \text{ rep} = 83 \text{ erg/gm. tissue.}$$

The individual beta rays from any single radioactive isotope may have any kinetic energy between zero and some maximum energy E_{max} million electron volts (Mev.) which characterizes the spectrum. For a large number of disintegrating atoms, there will be some average kinetic energy E_{av} Mev. per disintegrating atom, which can represent the beta-ray spectrum (E_{av} should include conversion electron lines if they are present). If we call C the local concentration of radioactive isotope in millicuries (mc.) per gram of tissue, and arbitrarily define the millicurie as 3.7×10^{7} disintegrating atoms per second, then the tissue dosage rate, R, may be written:

$$R = \left[\frac{3.7 \times 10^{7}\ C \text{ disint.}}{\text{sec. gm.}}\right]\left[\frac{10^{6}\ E_{av} \text{ e.v.}}{\text{disint.}}\right]\left[\frac{1 \text{ rep.}}{5.24 \times 10^{13} \text{ e.v./gm.}}\right]\left[\frac{60 \text{ sec.}}{\text{min.}}\right]$$

$$= 42.4\ CE_{av} \text{ rep/min. (for } C \text{ in mc./gm.)} \quad (1)$$

If the concentration of radioactive isotope is to be measured instead in rutherfords (rd) per gram of tissue (1 rd $= 10^{6}$ disintegrating atoms per sec),[12] then:

$$R = 1.15\ CE_{av} \text{ rep/min. (for } C \text{ in rd/gm.)}$$

Thus[6] for 12.6 hr. I^{130}, where $E_{av} = 0.29$ Mev., 1 mc./gm. delivers 12.3 rep/min. while for 8.0 day I^{131}, where $E_{av} = 0.20$, 1 mc./gm. delivers 8.5 rep/min.

The detailed shape of the beta-ray spectrum is known only for a very few isotopes, so very precise values of E_{av} are usually not known at present. Within an accuracy of perhaps ± 15 per cent, $E_{av} = E_{max}/3$ for all simple beta ray spectra and E_{av}/E_{max} is generally smaller for the isotopes which which have what are called "forbidden

* Presented at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

spectra" than for "allowed spectra." In the case of isotopes with compound beta-ray spectra, such as I^{130}, the values of E_{av} for each component of the beta-ray spectrum may be estimated separately, and then weighted in proportion to the relative abundances of the components, in order to obtain E_{av} for equation (1). For pure line-spectrum alpha ray emitters, such as polonium, E_{av} is simply the total energy of disintegration, i.e. the energy of the alpha ray plus the energy of the recoil nucleus.

The dosage rate R of equation (1) is usually to be regarded as a maximum value, corresponding to the dosage rate within a mass of tissue whose dimensions are greater than the range of the alpha or beta radiation, and in which the distribution of the radioactive isotope is uniform.

Representing E_{av} as $E_{max}/3$, equation (1) leads to an approximate rule-of-thumb which is often useful, namely: a concentration of one microcurie per kilogram produces about $E_{max}/50$ (rep/day). Alternatively: 1 mc./kg. gives about 20 E_{max} (rep/day), or:

$R = 60\ CE_{av}$ rep/day (C in μc/gm. or mc./kg.)

The activity of each pure radioactive isotope decreases exponentially with time, falling to half of any initial value in a time T, the so-called "half-period." Then the average life of all the radioactive atoms of a given species can be shown to be $1.44\ T$.

Then, if the isotope concentration C in mc./gm. has the values C_1 at time t_1 and C_2 at some later time t_2, and if no isotope was lost by excretion from the tissue, the total dosage delivered will be:

$$D = \int_{t_1}^{t_2} R\,dt = 1.44T(R_1 - R_2)\ \text{(rep)} \quad (2)$$

where the term $(R_1 - R_2) = 42.4\ E_{av}(C_1 - C_2)$, and T is in minutes because R is in rep/min. Here $(C_1 - C_2)$ can be thought of as millicuries-destroyed per gram of tissue.

If, as is usually the case, some isotope is absorbed or excreted by the tissue then C is no longer a simple exponential function of time, and equation (2) takes the form

$$D = \int_{t_1}^{t_2} FC_0 e^{-t/1.44T}\,dt \quad (3)$$

where F is the fractional amount of isotope present at any time, by virtue of biological processes, and $F = 1$ corresponds to the value of isotope concentration, C, used in equation (1), and occurs at a time t when:

$$R = 42.4CE_{av} = R_0 e^{-t/1.44T}. \quad (4)$$

In the usual case, total dosage must be determined by graphical or numerical integration of equation (3) (for example see Table 1 of reference 6).

It will be noted from equation (2) that a long-lived isotope (e.g. I^{131}), if retained by the tissues, delivers a total dose which is greater than the total dose from a short-lived isotope (e.g. I^{130}) if the two isotopes have the same initial dosage rates, R. Conversely, if a particular total dose, D, is to be given, the dosage rate, R, must be smaller if a long-lived isotope is used than if a short-lived isotope is used. Of course, identical biological effects cannot be expected from identical total doses, D, delivered at different rates.

Some radioactive isotopes[12] used for therapy (e.g. Mn^{52}) have very complicated nuclear spectra, involving orbital electron capture, complex gamma-ray spectra, internal conversion electrons, and continuous beta-ray spectra. In such cases, special attention must be given to the energy delivered by radiations other than the continuous beta rays.*

Massachusetts Institute of Technology
Cambridge 39, Mass.

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ARTIFICIALLY PREPARED RADIOACTIVE ISOTOPES AS A MEANS OF ADMINISTERING RADIATION THERAPY*

By EDWARD H. REINHARD, M.D.
Mallinckrodt Institute of Radiology
ST. LOUIS, MISSOURI

IN A recent article in Collier's magazine the theme of which was that the new chemotherapeutic agents are not quite the miracle drugs they were first heralded as being, Dr. O. H. P. Pepper of the University of Pennsylvania is quoted as having said: "Every new drug when it comes out goes through what looks like a typhoid fever curve. First the fever goes 'way up, while every doctor uses the drug for everything; then it goes 'way down, while the drug is universally condemned. Finally, the fever finds its level, and stays there.'[6]

Radioactive isotopes as therapeutic agents have definitely passed through the first two phases of such a curve, and the time has now arrived when it should be possible to re-evaluate these agents and "find their level."

Radioactive isotopes of only two elements, phosphorus and iodine, have been used extensively in the treatment of disease and proved to be of real value. The therapeutic use of these two elements will be discussed in detail. Brief mention will be made of the limited amount of work which has been done in various laboratories on the therapeutic use of radioactive isotopes of sodium, calcium, strontium, and manganese.

RADIOACTIVE PHOSPHORUS

The nature and properties of radioactive phosphorus, and the experimental work upon which the therapeutic use of this isotope is based have been reviewed in detail in previous publications.[1–7] We will discuss here only the most important properties and characteristics of P^{32}.

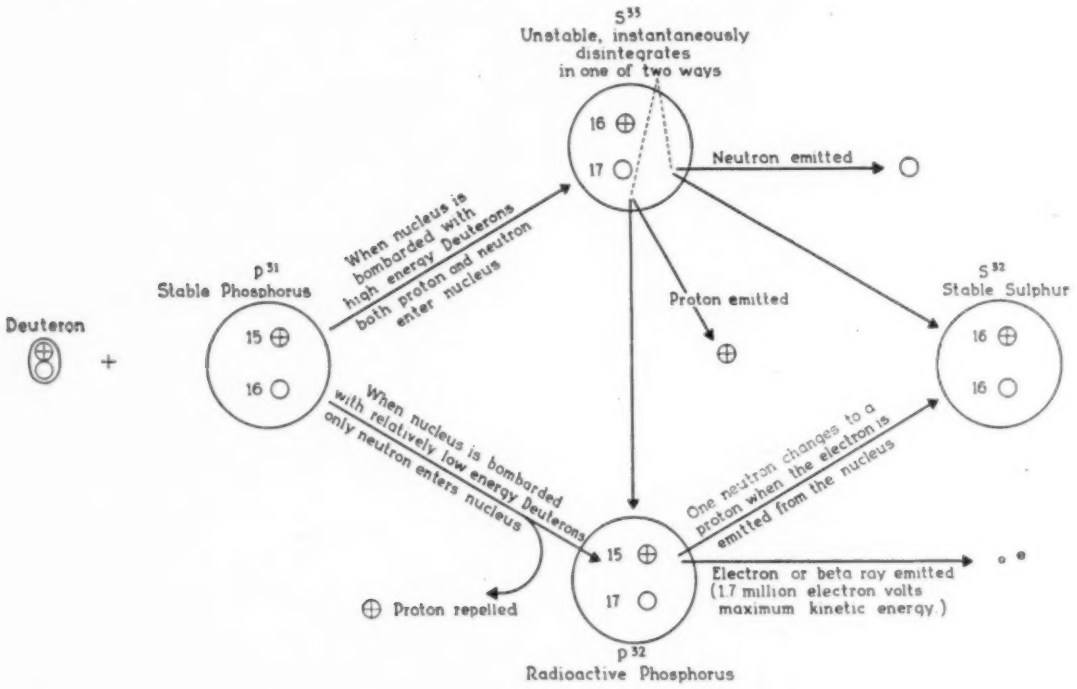
Figure 1 illustrates the nuclear changes involved in the production of radioactive phosphorus and its transformation into stable sulfur. The nucleus of stable phosphorus contains 15 protons and 16 neutrons giving a total mass of 31. When the nucleus is bombarded with energetic deuterons, one of two things may happen. When a nucleus is bombarded by a deuteron having an extremely high energy, both the proton and the neutron may enter the nucleus with resultant conversion of the atom into S^{33}. S^{33} is unstable and instantaneously disintegrates into stable sulfur (by the emission of a neutron), or into radioactive phosphorus (by the emission of a proton). On the other hand, when the nucleus of stable phosphorus is bombarded by a relatively low energy deuteron, only the neutron enters the nucleus while the proton is repelled. The new atom which is formed is radioactive phosphorus which has a mass of 32. Radioactive phosphorus disintegrates by the emission of an electron or beta ray whereupon one neutron disappears and a proton takes its place. Thereupon the radioactive phosphorus becomes stable sulfur.

The electron or beta ray which is emitted when P^{33} disintegrates is the means by which radioactive phosphorus exerts its effect on tissues. These beta rays have energies as high as 1.8 million electron volts; their average energy is approximately 0.6 million electron volts. The *maximum* range of penetration of these rays through the body tissues is approximately 0.7 centimeters. The half-life of P^{32} is 14.3 days.

Studies by various investigators have shown that when radioactive phosphorus is administered to animals or humans it is selectively withdrawn from the blood by certain tissues and cells. The tissues in

* Presented at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

which P^{32} accumulates in largest amounts are those tissues which are usually primarily involved in polycythemia vera, the leukemias, and the lymph node diseases. The amount of phosphorus taken up by leukemia than in the corresponding organs of normal mice. Figure 2 shows graphically the results of this study. A single dose of labeled phosphorus was administered to two groups of mice; one normal and one



Schematic presentation of nuclear changes involved in the production of radioactive phosphorus and its transformation into stable sulphur. Protons are marked with a plus because of their positive charge, while neutrons are left blank. The number of electrons which revolve about the nucleus: 1) is equal to the number of protons in the nucleus, 2) determines the chemical identity of the atom. Since both stable and radioactive phosphorus have 15 protons, they behave alike chemically.

FIG. 1. Radioactive phosphorus produced by deuteron bombardment of stable phosphorus (only nuclei are represented). Reproduced with permission of the Editor of the *Journal of Laboratory and Clinical Medicine*, 1946, *31*, 112.

any given tissue is dependent on the total phosphorus content of the tissue, the rate of phosphorus turnover by the tissue, and the rate at which new tissue is being formed. Thus, a relatively large portion of an administered dose of P^{32} always accumulates in the bone as the total phosphorus content of this tissue is high, and the cells in the marrow ordinarily multiply rapidly.

Studies by Lawrence and his associates[8] have shown that radioactive phosphorus is taken up much more rapidly and in two to three times larger amounts by the lymph nodes and spleens of mice with lymphatic with lymphatic leukemia. The animals were sacrificed at various intervals, and the labeled phosphorus content of the tissues was determined. The amount of radiophosphorus found in different organs is expressed in per cent of the administered dose present per gram of wet tissue. There was only slightly more P^{32} in the bone and liver of the leukemic mice than in these organs in the normal mice, but the lymph nodes and spleens of the leukemic animals took up from two to three times as much P^{32} as did these organs in the normal mice.

Tuttle and his associates[9] have demon-

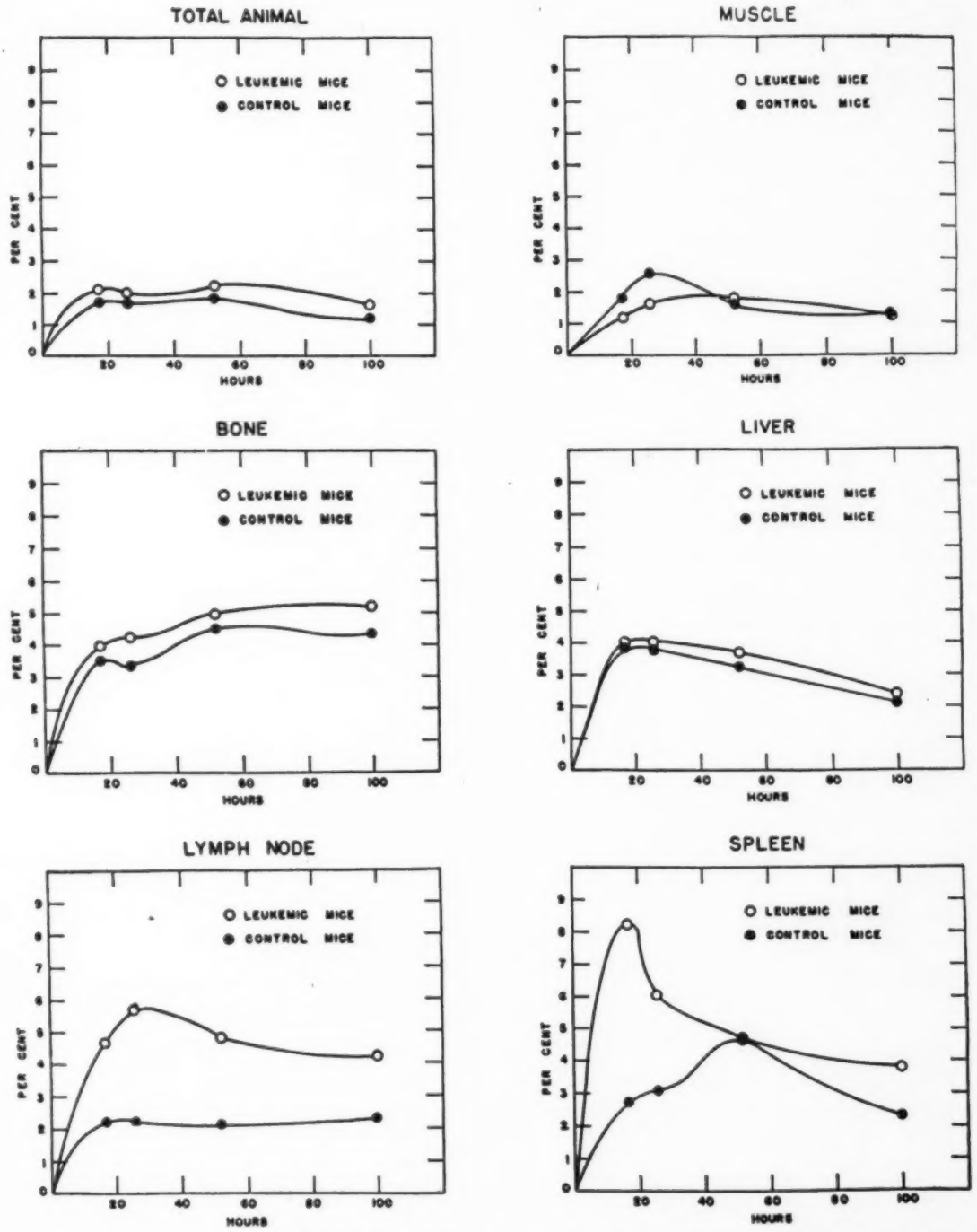


Fig. 2. Distribution of radiophosphorus in the tissues of normal and leukemic mice. Reproduced with the permission of Dr. John H. Lawrence from the *Journal of Clinical Investigation*, 1940, *19*, 267.

strated that most of this increased phosphorus content of the leukemic lymphoid organs is due to the greatly increased amount of P^{32} which accumulates in the nucleoprotein fraction of these tissues. Figure 3 shows the fate of a single dose of P^{32} given intraperitoneally to another large group of normal and leukemic mice. In this

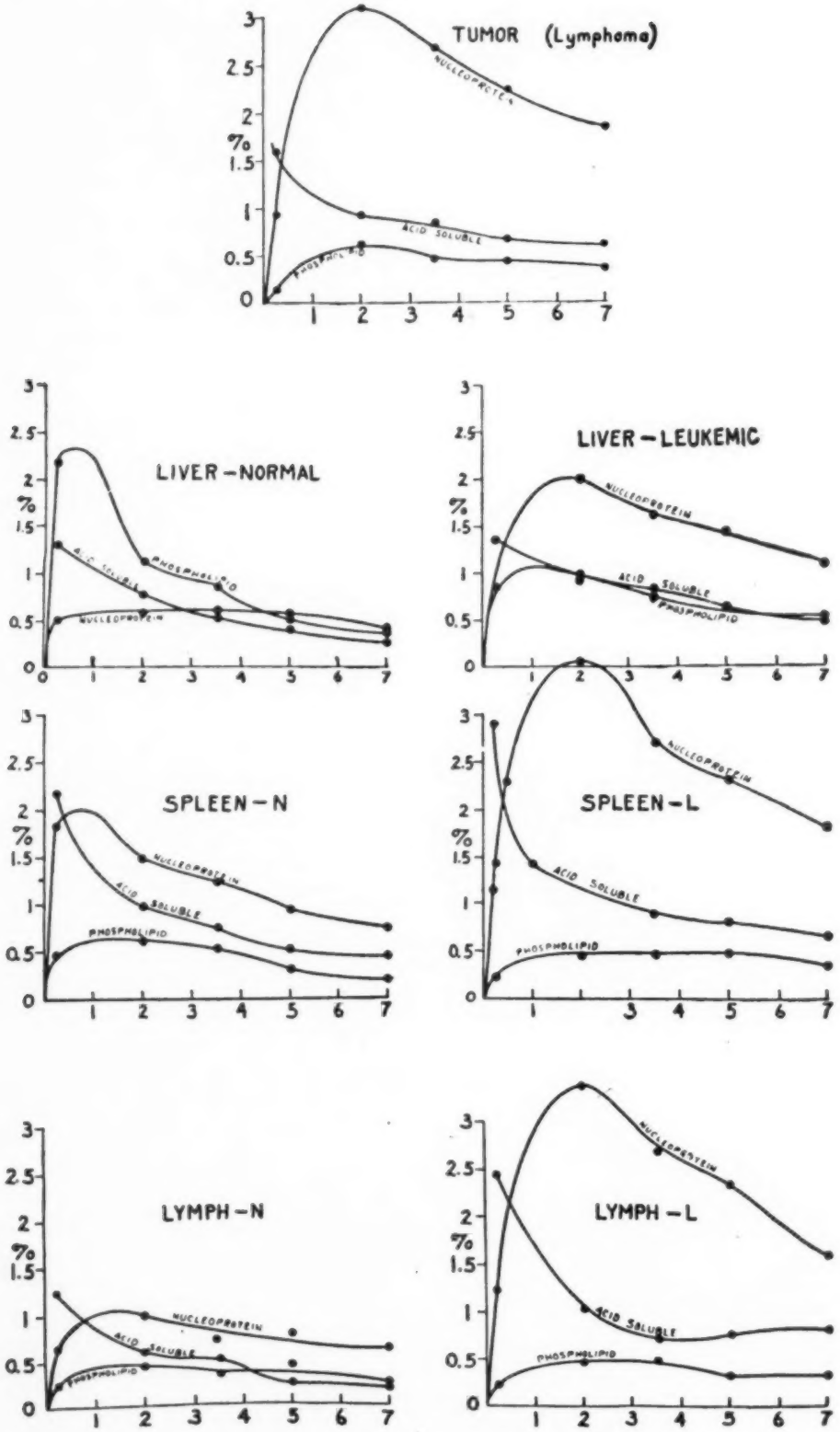


FIG. 3. The comparative uptake of labeled phosphorus in normal and leukemic mice. Reproduced with the permission of the authors[9] from the *Journal of Clinical Investigation*, 1941, *20*, 57.

experiment various tissues were removed at intervals after the injection, the different organic phosphorus fractions were chemically extracted, and the P^{32} content of each fraction was determined. The nucleoprotein fraction of lymph nodes, spleen, and tumor tissue from the leukemic mice contained much more P^{32} than did the nucleoprotein fraction of corresponding organs in the normal animals. Thus, phosphorus, including radioactive phorphorus if it is available, is taken from the blood stream and used in the synthesis of nucleoproteins at a much more rapid rate by the leukemic cells than by cells in the corresponding normal tissues.

Similarly, the distribution of radioactive phosphorus in the tissues obtained at autopsy of patients who have been treated with P^{32} has been studied by several groups of investigators. In leukemic patients the greatest concentrations of P^{32} have usually been found in the bone marrow, lymph nodes, spleen, and liver. These findings are in agreement with those previously described for leukemic mice. Many such determinations have been made in our laboratory. Table 1 illustrates the results of such analyses on 3 of our patients. The first patient had chronic myelogenous leukemia. The radioactivity of the various tissues is expressed in microcuries per gram of wet tissue calculated as of the time of death. In this particular case the bone marrow had three times as much radioactivity as any other organ. In chronic myelogenous leukemia the marrow usually has greater activity than any other organ, but this marked discrepancy between the activity of the bone marrow as compared to the liver and spleen is unusual. The next patient had leukosarcoma and in this case the activity of the liver and spleen was greater than that of the bone marrow. The last patient, who had multiple myeloma, showed the greatest activity in the tumor tissue. In spite of this he responded very poorly to treatment apparently due to the fact that the tumor cells are less sensitive to radiation than are normal marrow cells.

In the past there has been considerable confusion regarding the proper dosage of radioactive phosphorus for various diseases. Part of this confusion was due to the fact that there is considerable variation in the susceptibility of different patients to P^{32} just as in the case with roentgen rays.

Table I

RADIOACTIVITY OF TISSUES OBTAINED AT AUTOPSY
(Expressed in Microcuries per Gram of Wet Tissue)

	Patient: L. E. Chronic myeloid leukemia	Patient: M. T. Leuko-sarcoma	Patient: R. R. Multiple myeloma
Bone marrow	0.263	0.037	—
Lymph node	0.063	0.019	—
Spleen	0.081	0.053	0.066
Liver	0.088	0.098	0.102
Kidney	0.061	--	0.059
Muscle	0.020	0.024	—
Brain	—	0.012	0.008
Intestine	—	—	0.031
Tumor	—	—	0.108

However, there is another factor involved. We sent samples of radioactive phosphorus to several laboratories where this isotope is being used extensively, and to the National Bureau of Standards, and compared the figures obtained in our laboratory with the figures obtained when the sample was assayed in these institutions. Widely divergent values were obtained. As a result of this disturbing discrepancy, Dr. Martin Kamen of the Mallinckrodt Institute re-evaluated the standard that we had been using and concluded that it was in error by a factor of 2.3. The National Bureau of Standards' figures were correct, and it would help greatly to clear up this source of confusion if all institutions who are assaying isotopes for therapeutic use would check their standards with the Bureau. I want to emphasize that all dosage figures given in our previous publications must be multiplied by 2.3 to convert to the corrected millicurie which we now use. The dosages given in this paper are expressed in the corrected millicurie.

Next, we will consider the therapeutic results which have been obtained in the treatment of various blood dyscrasias, lymphomas, and other malignant neoplastic diseases with radioactive phosphorus. The various disorders for which this treatment has been tried will be considered in the approximate order of its effectiveness.

Polycythemia Vera. There are eight papers in the medical literature which describe clinical results obtained in the therapy of polycythemia with radioactive phosphorus. These papers are based on a study of 78 patients. There is substantial agreement in all these reports that excellent clinical and hematologic remissions can be obtained in the majority of patients.

During the last four and one-half years, 43 patients with polycythemia vera have been treated with P^{32} at the Mallinckrodt Institute. All of these patients are now either asymptomatic or at least markedly improved except 2 who have died. One of the deaths was due to suicide, and the other patient died with the blood and bone marrow findings of myelogenous leukemia.

Figure 4 illustrates the response to P^{32} therapy in a sixty-five year old woman with polycythemia vera. Her symptoms began in January, 1940, and consisted of fatigability, anginal pains, a feeling of fullness and occasional pain in the left upper quadrant, intense itching, and weight loss. Physical examination revealed a blood pressure of 185/115, a ruddy complexion with moderate cyanosis, marked splenomegaly and slight hepatomegaly.

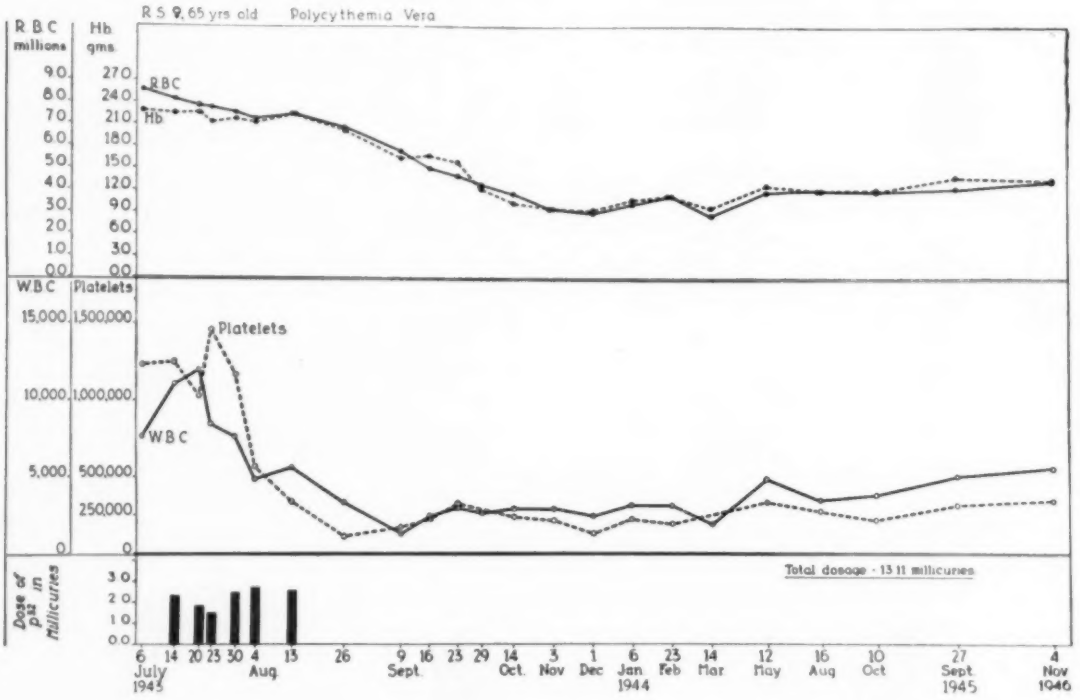


FIG. 4

The erythrocyte count just before treatment was started in July, 1943, was 8,110,000; the hemoglobin value was 22.3 grams; the leukocyte count was 11,100; and the platelets, 1,230,000. During a period of four weeks the patient was given 13 millicuries of P^{32}. The leukocyte count and the platelet count began to fall about a week after treatment was started, but the erythrocyte count showed no significant drop until about a month after the beginning of therapy. Three months later the patient had a slight anemia (red count about 4,000,000) as well as a well marked leukopenia and thrombocytopenia. Symptomatically she was greatly improved

at this time. The blood counts very slowly increased until a year after the treatment the red cell count, the leukocyte count, and the platelet level were all normal. She has had no symptoms since September, 1943, except occasional pains in the shoulders and arms attributable to cervical arthritis. In December, 1946—three and one-half years since her first course of treatment—her blood was still normal in all respects. This patient was obviously overtreated, and we now recommend from 6 to 8 millicuries for the first course of treatment. However, this case illustrates clearly the prolonged remissions which can be obtained with P^{32} therapy.

Several features regarding the response of patients with polycythemia to P^{32} therapy need to be emphasized. First, there is marked variation in the response of different patients to the same dosage of radioactive phosphorus. A dosage which produces perfect control of polycythemia in one patient may produce profound anemia in another patient. In general, the heavier the patient and the greater the severity of the disease, the larger will be the required dosage, but the exact amount required to restore the blood counts to normal in any particular case cannot be predicted in advance. Second, the erythrocyte count never shows a significant decrease in less than three weeks and the latent period is frequently considerably longer than this. It is usually two to three months after treatment is started before the red blood cell count becomes stabilized at a new (lower) level. Thus it is desirable to allow two or three months to elapse after the first injection before deciding if further injections are needed. The last point I wish to emphasize is that hematologic and symptomatic remissions produced by P^{32} therapy have lasted anywhere from five months to more than four years in our patients. The average interval before a second course of treatment is required is about thirteen months.

Careful study of the patients who have been treated at the Mallinckrodt Institute revealed that all patients who had headaches, dizziness, or lacrimation and burning of the eyes were at least partially relieved of these symptoms, whereas fatigability, aching pain in the extremities, and itching were at least partially relieved in more than 90 per cent of the patients having these symptoms. Cyanosis disappeared in all the patients who had this finding, and the spleen and liver invariably decreased in size.

It is not possible to draw any conclusions from the data now available regarding the effect of P^{32} therapy on the duration of life of patients with this disease. Furthermore, these patients have not been followed for a sufficiently long period of time to permit a comparison of the duration of life of patients treated with P^{32} with the duration of life in individuals treated with roentgen rays or by phlebotomies.

Myelogenous Leukemia. There are ten reports in the literature dealing with the therapeutic effectiveness of radioactive phosphorus in myelogenous leukemia. All investigators have agreed that P^{32} is of little or no value in the treatment of acute myelogenous leukemia. There is also agreement that in chronic myelogenous leukemia administration of radioactive phosphorus will usually restore the leukocyte count to normal or approximately normal levels, and that a rise in the erythrocyte count frequently follows. This hematologic improvement is quite consistently accompanied by definite symptomatic improvement.

Figure 5 illustrates the hematologic response to P^{32} therapy in a thirty-five year old woman. She had had fatigability and numerous large, spontaneous bruises for about three months when we first saw her in September, 1943. The leukocyte count at that time was 175,000; the erythrocyte count was 3,480,000; and the differential revealed 27 per cent metamyelocytes and 14 per cent myelocytes. During the first three years of treatment she received 33 injections of P^{32} totalling 69.3 millicuries. She is at present (January, 1947) asymptomatic. The leukocyte level has remained below 20,000 except for a few isolated counts throughout this interval, and the red cell and thrombocyte levels have remained higher than they were prior to treatment. No transfusions have been given.

Analysis of the 51 cases treated at the Mallinckrodt Institute shows that weakness, by far the most common symptom, was completely or partially relieved in about 90 per cent of the patients. All other common symptoms except nervousness and anxiety were completely relieved in at least 50 per cent of the patients. Abnormal physical signs including fever, petechiae, bleeding from the nose and gums, enlarged lymph nodes, splenomegaly and hepatomegaly disappeared or partially subsided in at least two-thirds of the cases.

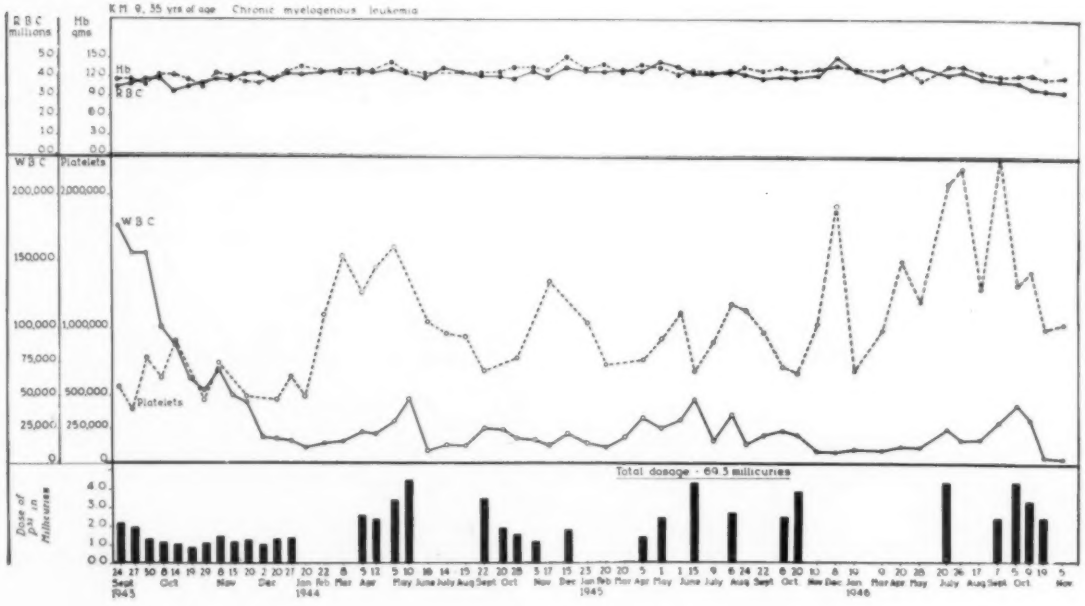


FIG. 5

An important problem which remains to be answered is the effect of P^{32} on the duration of life of patients with myelogenous leukemia. Minot, Buckman and Isaacs[10] have reported the average duration of life from the first symptom until death in a large series of patients who received no radiation was 3.0 years, and in another series of patients treated with roentgen radiation was 3.5 years. The average duration of the disease from the onset of symptoms until death in our patients who have already died was 3.6 years. All patients with myelogenous leukemia seen in our clinic during the period of this study were treated with P^{32}, whether the disease was acute or chronic, early or terminal. Some of the patients lived only two to three days after treatment was started, and these were included in our series. It appears, therefore, that P^{32} therapy prolongs life by only a few months, and there is no significant difference in this regard between P^{32} and roentgen therapy. Both forms of therapy definitely prolong the period of useful, relatively symptom-free life.

Lymphatic Leukemia. There are eleven reports in the literature dealing with the therapeutic effectiveness of radioactive phosphorus for lymphatic leukemia. Most of these investigators agree that P^{32} is effective in the majority of cases of chronic lymphatic leukemia in restoring the leukocyte count to near normal levels, reducing the size of enlarged lymph nodes and spleen, and temporarily relieving symptoms. Data presented by Erf and his associates,[11] a report by Craver,[12] and our own experience all indicate that P^{32} is somewhat less effective in chronic lymphatic leukemia than in chronic myelogenous leukemia.

However, Warren[13] found a higher percentage of his patients with chronic lymphatic leukemia were helped by this treatment than was the case among his patients with chronic myelogenous leukemia.

Figure 6 illustrates the results of therapy in a fifty-eight year old coal miner with chronic lymphatic leukemia. He developed weakness and fatigability in August, 1942, and in November, 1942, he began to have aching pain in the left upper quadrant of the abdomen. On physical examination in October, 1942, he was found to have moderate enlargement of the cervical, axillary, and inguinal lymph nodes, and the spleen extended 8 cm. below the costal margin. The leukocyte count at that time was 40,300; the erythrocyte count was 4,060,000; the platelet count was 382,000; and 81 per cent of the white blood cells were lymphocytes.

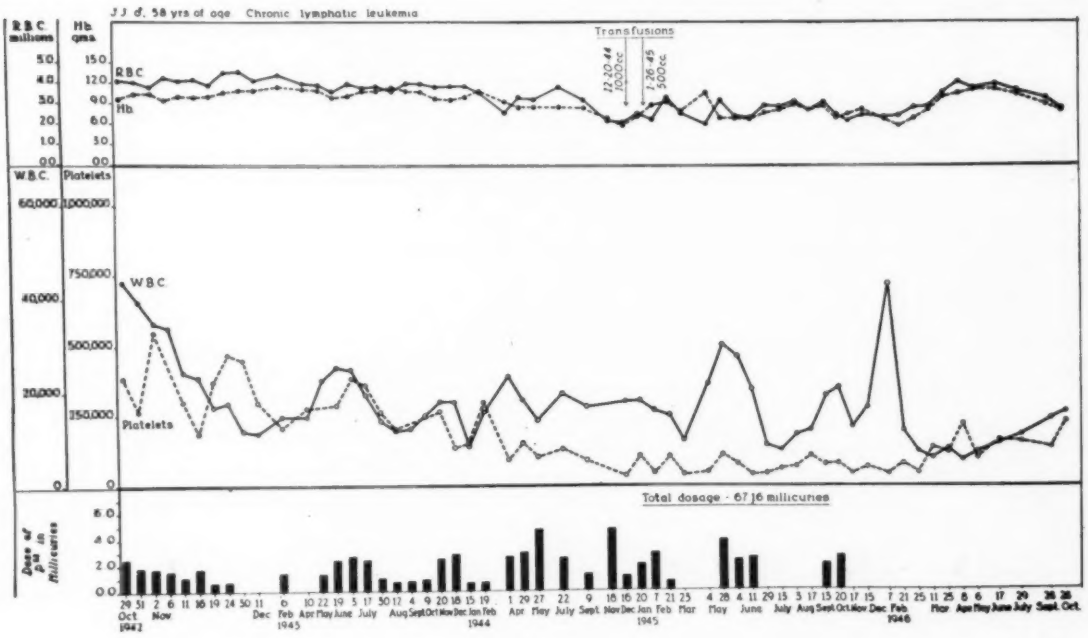


FIG. 6

Two weeks later he was found to have petechiae, bleeding from the nose and gums, and weakness. His platelet count has been below 100,000 ever since then. He was still alive in December, 1946, but for the last two years has been unable to work and has required repeated transfusions.

Analysis of the data on 47 cases of chronic lymphatic leukemia treated at the Mallinckrodt Institute shows that there was less striking symptomatic relief in this group than in the chronic myelogenous group. Furthermore, a significant decrease in the size of the lymph nodes, spleen and liver following therapy was less common in the patients with chronic lymphatic leukemia than in the patients with chronic myelogenous leukemia.

In any type of chronic leukemia, roentgen radiation is more effective in some cases than P^{32} in bringing about a rapid reduction in the size of the spleen or lymph nodes. Therefore, roentgen therapy should be used whenever the prompt reduction of nodes or the spleen is necessary to relieve symptoms or remove pressure on some vital organ. Roentgen irradiation may be used to supplement radioactive phosphorus for this purpose.

Other Diseases. Radioactive phosphorus has not been found to be of any value in

the treatment of any of the acute forms of leukemia. None of the 10 cases of monocytic leukemia which we treated showed any improvement.

Various investigators have reported a few cases of Hodgkin's disease, lymphosarcoma, and multiple myeloma in which improvement occurred following P^{32} therapy. In our experience none of these conditions respond as favorably to radioactive phosphorus as they do to roentgen therapy. A few cases of lymphoepithelioma, malignant melanoma, carcinoma of the gallbladder, carcinoma of the breast, Ewing's tumor, mycosis fungoides, and xanthomatosis have been treated with P^{32} at the Mallinckrodt Institute and in other clinics. There is no convincing evidence that this treatment is of any value in any of these neoplastic diseases.

Summary. In our opinion radioactive phosphorus is of proved value only in polycythemia vera and the chronic forms of leukemia.

We consider P^{32} the most effective therapeutic agent available at the present time for polycythemia vera. Complete hematologic and almost complete symptomatic remissions can be produced with P^{32} in the vast majority of patients, and remission from a single course of treatment may last for from six months to three and one-half years or longer with an average of about thirteen months.

P^{32} therapy produces at least as complete clinical and hematologic remissions as roentgen irradiation in chronic myelogenous leukemia. Radioactive phosphorus treatment has the practical advantage of complete freedom from radiation sickness. The duration of life from the first symptom until death of the patients treated at the Mallinckrodt Institute suggests that P^{32} therapy prolongs life to approximately the same extent as does roentgen therapy (about six months).

In the treatment of chronic lymphatic leukemia, P^{32} is probably as satisfactory as, but no better than roentgen irradiation. Roentgen irradiation is the preferred treatment when rapid reduction in the size of enlarged lymph nodes and spleen is important.

In our experience, P^{32} has not proved to be of value in any of the other conditions for which it has been tried.

RADIOACTIVE IODINE

Most of the preparations of radioactive iodine which have been used therapeutically have consisted of a mixture of two isotopes, I^{130}, which has a half-life of 12.6 hours, and I^{131}, whose half-life is eight days. Radioactive iodine is prepared by deuteron bombardment of metallic tellurium in a cyclotron, or it can be prepared in a pile. Immediately after a short bombardment the twelve hour iodine has about ten times the radioactivity of the eight day iodine isotope which is produced simultaneously. With longer bombardments, the ratio of eight day iodine to twelve hour iodine increases. Following the bombardment, the iodine is chemically separated from the tellurium and is converted into sodium or potassium iodide. The final solution which is administered to patients consists of the radioactive sodium iodide plus non-radioactive carrier sodium iodide in distilled water.

I^{130}, the twelve hour isotope, and I^{131}, the eight day isotope, both emit beta rays and gamma rays. From the standpoint of the effect on tissues, the beta rays are the more important.

Accumulation of Radioiodine in the Thyroid Gland. Hertz and his associates[14,15] were the first to study the rate at which radioiodine is accumulated in the thyroid gland. They found that in rabbits, significant accumulation of iodine in the thyroid gland occurs within a few minutes after administration of the tagged element. They also found that the uptake was much greater in thyroids which had previously been rendered hyperplastic. The normal thyroid was found to collect up to 80 times the quantity to be expected from uniform diffusion into the general body tissues; the

hyperplastic thyroid collected up to several hundred times the quantity expected from uniform diffusion.

Hamilton and Soley[16,17] showed that in humans the same principles apply. They compared the uptake of labelled iodine by the thyroids of normal controls and of patients with various types of thyroid disease in situ. This was done by placing a Geiger counter tube against the neck directly over the thyroid gland and taking readings at various intervals after the administration of a single dose of labelled iodine. None of these individuals had received iodine before the radioisotope was given. Figure 7 shows the uptake curves which they obtained when 14 mg. of iodine was given as sodium iodide which was labelled with radioiodine.

Hamilton and Soley[18] then repeated these experiments under the same conditions with the exception that each subject received a test dose which contained a total of approximately 0.1 microgram of iodine as sodium iodide. Figure 8 shows the uptake curves. A marked increase in uptake occurred in all four clinical types. This is what you would expect as the total iodine content of the thyroid is relatively small and its capacity to accumulate iodine is limited. Note that toxic goiters not only accumulated a larger percentage of the administered dose, but also retained it for much longer periods of time when the dose of iodide was small. This emphasizes the importance of avoiding excessive dilution of the radioactive substance with stable iodide when the material is used therapeutically.

Therapeutic Results. Hertz and Roberts[19] recently published a three to five year follow-up on 28 patients with hyperthyroidism treated with therapeutic doses of radioactive iodine. The radioiodine they used consisted at the time of administration of over 90 per cent twelve hour isotope and the remainder of the eight day isotope. The material was given *orally*. Because of the experimental work which we have just summarized, they kept the total amount of iodide administered below 2 mg. of iodide.

Of the 28 patients in this series, 5 subsequently had a subtotal thyroidectomy. All 5 of these patients developed "hypometabolism." In the remaining 23 cases no operation was performed. Three to five years after treatment 20 of these patients were no longer thyrotoxic. The thyroid decreased in size in all of these patients, and in all but three the gland became no longer palpable. No undesirable radiation effects were observed in any of these patients. Although 5 of the 20 patients who were not operated on developed basal metabolic levels of −15 to −20 per cent, none of them developed permanent myxedema.

From an analysis of their data Hertz and Roberts arrived at the following recommendations and conclusions:

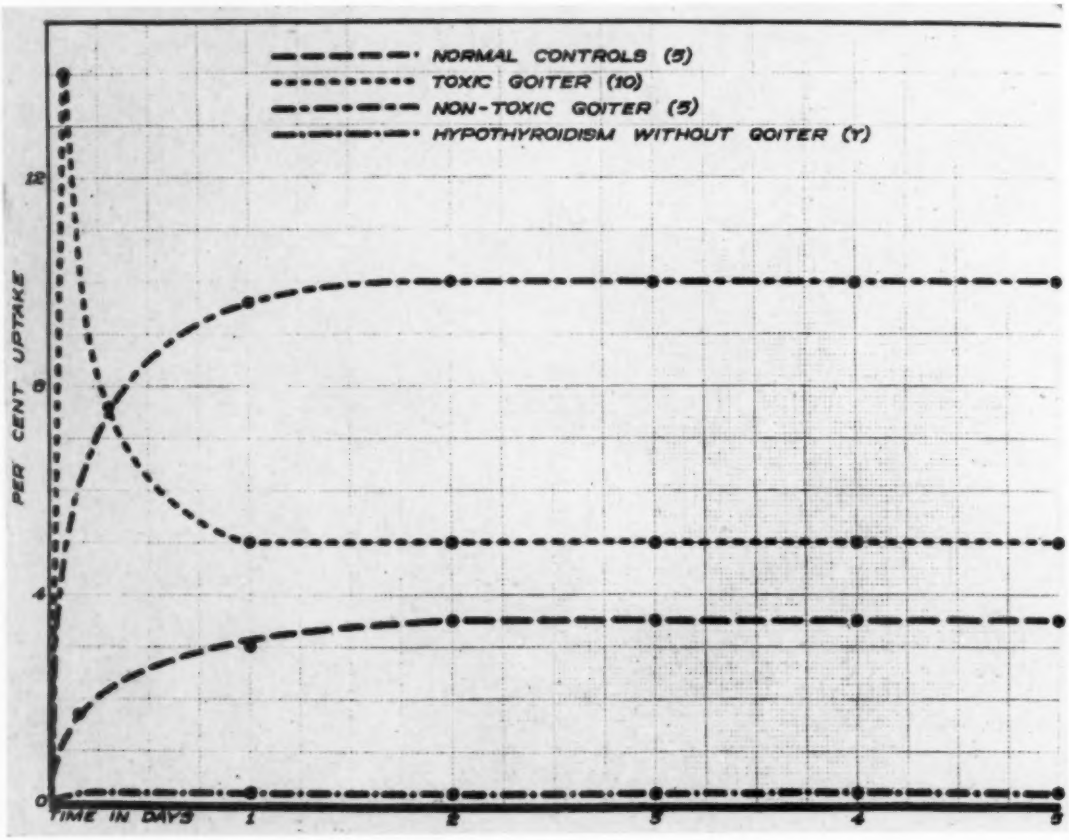
1. No patient should be treated with radioiodine if he has had previous routine iodine therapy unless such treatment has been stopped for at least one month prior to administration of the isotope.

2. It is unwise at present to treat patients having large goiters with secondary involutional changes with radioiodine as surgery might be needed on a purely mechanical basis even though detoxification by radioiodine could be accomplished.

3. These investigators advocate routine iodinization, starting one to three days after the administration of radioiodine, or as soon as the uptake is known to be adequate.

4. In their experience the therapeutically effective dosage range is from 5 millicuries to 25 millicuries given as a single dose. The choice of the dose is based largely on clinical estimation of the size of the goiter being treated.

Chapman and Evans[20] have also published a recent report on the treatment of hyperthyroidism with radioactive iodine. Their paper was based on a study of 22 cases. The solution they used, like that of Hertz and Roberts, contained about 90 per cent twelve hour isotope and 10 per cent eight day isotope. Figure 9 is taken from their paper, and illustrates the results obtained. This man had classic signs and


NORMAL CONTROLS (5)
TOXIC GOITER (10)
NON-TOXIC GOITER (5)
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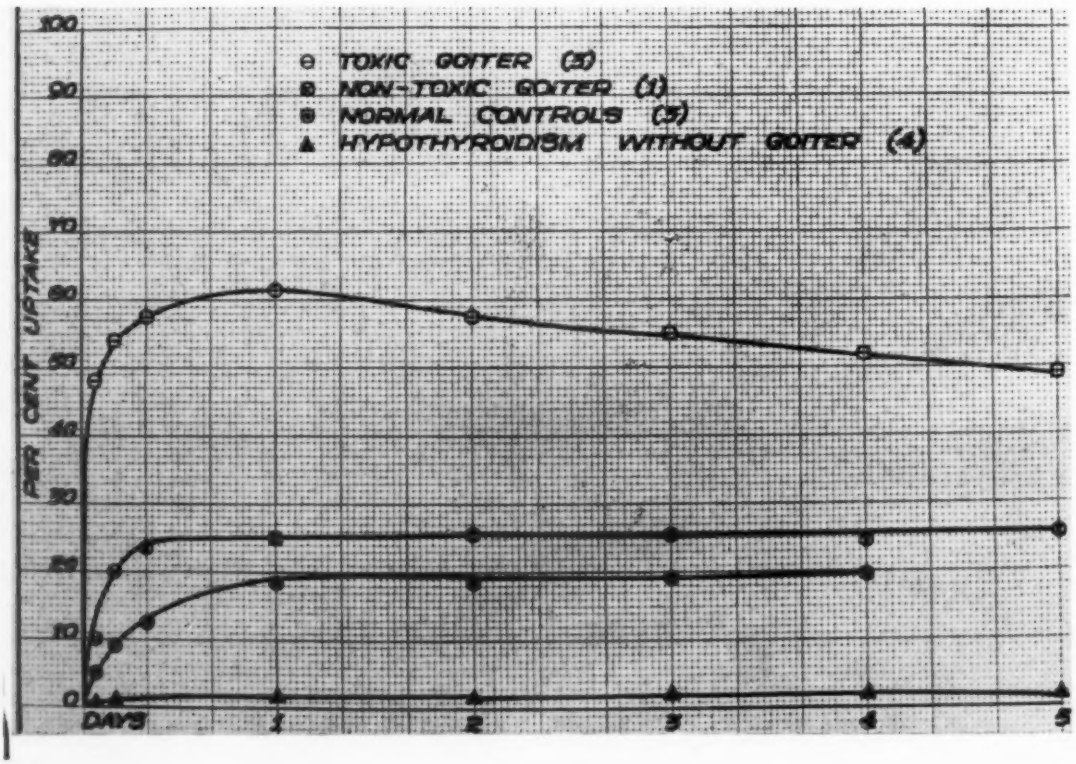
TOXIC GOITER (3)
NON-TOXIC GOITER (1)
NORMAL CONTROLS (3)
HYPOTHYROIDISM WITHOUT GOITER (4)
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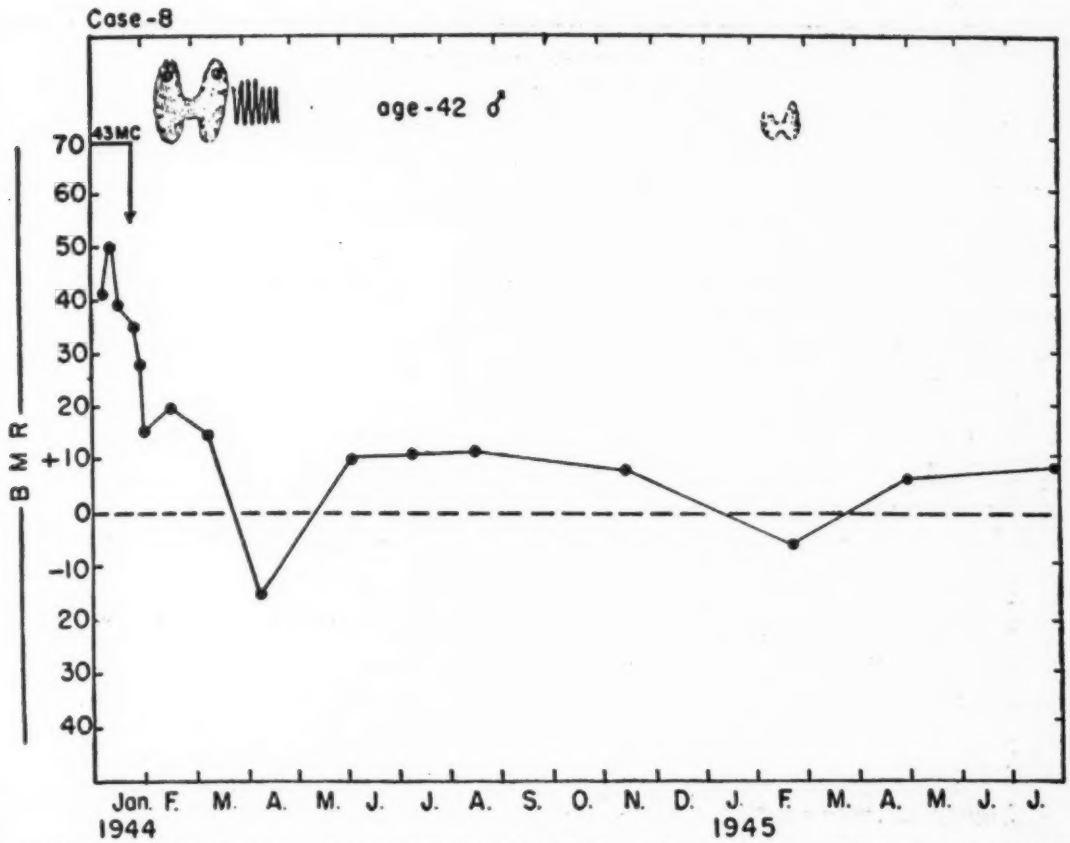

Fig. 9. Reproduced with the permission of Dr. Earl M. Chapman from the *Journal of the American Medical Association*, 1946, *131*, 90.

symptoms of moderately severe hyperthyroidism of six months' duration. The thyroid was symmetrically enlarged to about three times normal size. The basal metabolic rate was +44 and +52. On January 19, 1944, he drank 48 cc. of a solution containing 43 millicuries of radio-iodine. That evening he was nauseated and next day his temperature rose to 102°F. By January 21 his temperature returned to normal and he felt much better. His hyperthyroidism subsided progressively, and a year and a half later his basal metabolic rate was still within the normal range.

Chapman and Evans employed considerably larger doses than did Hertz and Roberts. The average total dose Chapman and Evans gave their patients was 40 to 50 millicuries, and the largest single dose given was 79 millicuries. Myxedema developed following treatment in 4 patients, and 2 patients, although improved after treatment, still had mild hyperthyroidism. Reactions which resembled roentgen sickness were observed in 6 patients following large doses of radioactive iodine. Several patients who had not responded well to thiouracil or routine lugolization subse-

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Fig. 7 and 8. Uptake of radio-iodine by the intact thyroid glands of normal human subjects and of patients with different types of thyroid disorders. In the experiment shown in Figure 7 (above), each subject received 14 mg. of iodine as sodium iodide which was labelled with radio-iodine. In the experiment represented by Figure 8 (below), each subject received a total of only 0.1 of a microgram of iodine as sodium iodide which was labelled with radio-iodine. Reproduced with the permission of Dr. Joseph G. Hamilton from *Radiology*, 1942, *39*, 555.

quently responded well to radioactive iodine. Chapman and Evans do not recommend ordinary iodine therapy following administration of radioactive iodine; they consider this unnecessary.

Treatment of Carcinoma of the Thyroid. When radioiodine first became available it was hoped that this substance might offer an effective method of treating cancer of the thyroid. Obviously, if thyroid carcinoma cells selectively accumulate radioiodine, it should be possible to effectively irradiate not only the primary tumor but all the recognized and unrecognized metastases by simply giving a few intravenous injections. With this in mind, Hamilton and Soley[18] studied the localization of radioiodine in the cancerous thyroid tissue of 4 patients. Their results indicated that the malignant portions of the thyroid had no significant capacity to take up iodine. Table II illustrates the relative uptake of radioiodine by the normal thyroid tissue as compared with the malignant thyroid tissue in 2 of these patients after oral administration of 14 mg. of iodine containing radioiodine. The cancerous tissue took up very little of the labeled iodine, and metastatic tumor tissue took up even less.

These observations have now been amply confirmed by other investigators. The more malignant and anaplastic a thyroid cell becomes, the more completely it loses the ability to take up and utilize iodine. Rhoads[21] recently made the statement that "certainly not more than 15 per cent of all thyroid cancers have been shown to pick up appreciable amounts of radioactive iodine."

However, an occasional thyroid cancer does utilize iodine. Marinelli, Leiter and Seidlin studied a patient some years ago who had had a thyroidectomy for carcinoma (discussed by Rhoads[21]). Following removal of the gland the patient continued to show manifestations of hyperthyroidism. As the thyroid gland itself had been completely removed this was clear evidence that metastases were utilizing iodine to synthesize thyroxin. Tracer doses of iodine were given and when a Geiger counter was passed over the body metastases were detected which had not been visualized by ordinary roentgen-ray methods. The patient was then given a therapeutic dose of radioiodine and marked clinical improvement occurred. Several years later the patient was still alive and the tumor appeared to be no longer active. It should be kept in mind that this type of therapy is

Table II

RADIO-IODINE UPTAKE OF THE THYROIDS AND OF TUMOR TISSUE IN 2 PATIENTS WITH CARCINOMA OF THE THYROID AFTER ORAL ADMINISTRATION OF 14.0 MG. IODINE CONTAINING RADIO-IODINE

Diagnosis	Total Weight of Tissue, Gm.	Total Iodine in Tissue, Mg.	Radio-Iodine Uptake in Tissue, Per Cent	Iodine per Gram of Tissue, Mg.	Radio-Iodine Uptake per Gram of Tissue, Per Cent
Carcinoma of Thyroid					
A. Thyroid tissue	5	1.2	1.2	0.24	0.24
B. Cancerous tissue	138	<0.2	0.13	<0.002	0.001
C. Regional metastases	139	<0.2	0.05	<0.002	0.0004
Carcinoma of Thyroid					
A. Normal thyroid tissue	20	9.0	4.5	0.45	0.23
B. Cancerous tissue	90	<0.2	0.2	<0.002	0.0022

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effective in only one rather rare form of thyroid tumor, and the vast majority of thyroid cancers are totally unaffected by radioiodine.

INSOLUBLE COLLOIDAL SUSPENSIONS OF RADIOACTIVE ISOTOPES

Jones, Wrobel and Lyons[22] injected a colloidal suspension of insoluble chromic phosphate prepared from radioactive phosphorus into laboratory animals and found that the material was selectively concentrated in the reticuloendothelial cells of the body. The highest concentrations were found in the liver, spleen and bone marrow. These studies suggested the possibility of using some such preparation in the treatment of Hodgkin's disease, reticulum cell sarcoma and other tumors arising in the reticuloendothelial system. Since then radioactive chromic phosphate as well as radioactive iron phosphate have been given to a few human patients with various lymphomas with equivocal results.

Allen, Hempelmann and Womack[23] at the Mallinckrodt Institute of Radiology injected a suspension of radioactive chromium phosphate around the periphery of transplanted spontaneous mammary adenocarcinomas in mice. In most of the animals this treatment was followed by complete disappearance of the tumors. A few human patients with basal cell carcinoma of the face were similarly treated with very satisfastory results. These investigators emphasized that this type of tumor can be readily cured by surgery or roentgen therapy, and their interest in radioactive chromic phosphate was purely experimental.

Hahn[24] has recently been studying the effect of intravenously administered colloidal suspensions of manganese dioxide containing radioactive manganese in the treatment of Hodgkin's disease, chronic lymphatic leukemia, monocytic leukemia, reticuloendotheliosis, and lymphosarcoma. Manganese 52 has a half-life of 6.5 days but when the isotope is prepared in a cyclotron a small amount of manganese 54 with a half-life of 310 days is always produced. Manganese can be dispersed in a colloidal sol of ultramicroscopic particle size using gelatin as a supporting colloid. Inspection of the sol in an ultramicroscope shows definite brownian movement. The particles are therefore much smaller than colloidal chromic phosphate particles and Hahn believes this favors a more efficient and even phagocytosis of the material by reticuloendothelial cells throughout the body. Manganese is prepared by bombarding chromium, and it can be chemically separated from the chromium. As the manganese salt which is given to the patient is carrier-free, the actual amount of the element employed is so minute as to be well below the toxic range. Hahn states that early therapeutic results have shown promise, but the work is still in the preliminary stage. More recently Hahn has been carrying out similar investigations using radioactive gold sols.

RADIOACTIVE ISOTOPES OF CALCIUM AND STRONTIUM

The administration of radioactive calcium has been suggested as a means of irradiating certain bone tumors. This has not proved practical because of the difficulty of preparing radioactive isotopes of calcium and because of the relatively low energies of the radiations emitted. Strontium is physiologically interchangeable with calcium and an isotope of strontium which emits energetic beta rays can be prepared with relative ease. This has been employed in the treatment of bone tumors.[25] The radioactive strontium is accumulated in large amounts in those portions of the bone where active cell multiplication is taking place such as at the epiphyses and also at the site of fractures. Osteogenic sarcoma tissues will take up some of the isotope but the clinical results have been very disappointing and this type of therapy has been abandoned.

RADIOACTIVE SODIUM

Isotopes of sodium have been tried in the

treatment of leukemia. Na^{24} is the isotope which has been commonly employed. It has a half-life of 14.8 hours and emits both beta rays and gamma rays. Tremendous quantities of Na^{24} can be prepared by a very short bombardment. This element is distributed evenly to the tissue fluids throughout the body and there is no selective uptake by bone or bone marrow. However, chronic leukemia will respond favorably to radioactive sodium therapy just as it responds to general body roentgen radiation. Radioactive sodium is easy to prepare and inexpensive.

CONCLUSIONS

The hope that various inorganic elements might be taken up by malignant cells in such vastly greater amounts than by normal cells, that cancer could be effectively treated by administering the radioactive isotopes of these elements to patients has materialized to only an extremely limited extent. Work is now in progress on the selective concentration in cancer cells of a multitude of organic compounds such as amino acids, hormones, and so forth. These organic compounds can be synthesized from radioactive elements. Thus, the search goes on for a therapeutically effective means of selectively irradiating cancer cells without seriously damaging surrounding normal tissues.*

600 South Kingshighway
St. Louis 10, Mo.

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* For discussion see page 779.

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COMPARATIVE THERAPEUTIC EFFECTS OF RADIOACTIVE AND CHEMICAL AGENTS IN NEOPLASTIC DISEASES OF THE HEMOPOIETIC SYSTEM*

By AUSTIN M. BRUES, M.D., *and* LEON O. JACOBSON, M.D.
Department of Medicine, University of Chicago and Argonne National Laboratory
CHICAGO, ILLINOIS

RADIATION is but one of many agents having specific action on the blood-forming system. The present report will deal briefly with a number of chemical agents which have a measure of effectiveness in the treatment of diseases of this system, and in somewhat greater detail with the action of radioactive phosphorus and the alkylamines.

Arsenic. Historically, arsenic appears to be one of the oldest chemotherapeutic agents which has stood the test of time.[14] Forkner[5] considers that arsenic is of chief clinical value in chronic myeloid leukemia given as Fowler's solution in doses of 5 to 10 or more minims daily. It has a positive effect in chronic lymphatic leukemia, but in this disease its effectiveness is generally agreed to be much less than in myeloid leukemia.

The precise mode of action of arsenic in leukemia is uncertain. It is known that arsenic is an agent which arrests cell division, and is an enzyme inhibitor, particularly of enzymes containing the sulfhydryl group. In accordance with current trends in pharmacologic thought and in analogy with other agents which will be discussed, it seems likely that the action of arsenic on enzymes is important in this connection. It is known that arsenic is concentrated in blood cells and in bone marrow, but other organs show equally high concentrations, including bone and skin. In fact, the diagnosis of chronic arsenical poisoning can be made by analysis of hair for arsenic. Arsenic is a mild carcinogenic agent, producing keratoses of the skin after long administration, which may be the precursors of cutaneous carcinoma.

Benzol. Another agent with a marked and specific action on hemopoietic tissue, particularly myeloid tissue, is benzol. Because of its importance as an industrial hazard, its toxicity to bone marrow is well known. It may cause aplastic anemia, or it may cause an overcompensation in the form of myeloid metaplasia in extramedullary organs. Myeloid metaplasia can be almost indistinguishable from myeloid leukemia, clinically and hematologically, and indeed pathologists may be doubtful as to the correct diagnosis. As an end result, myeloid leukemia may follow chronic benzol intoxication, and this may bear an analogy to the experimental production of lymphoid leukemia following total body roentgen irradiation.

Benzol is undoubtedly effective in relieving leukemia, but it is not in common use at present in this country. The reasons given for its neglect are that its toxic and effective doses are closer together than in the case of other agents, and particularly that there is great individual variability in response. Certainly, fatal myeloid metaplasia may be seen following relatively minor exposures in susceptible individuals.[18]

Other Agents. Certain other agents deserve comment, on behalf of which there is some recent evidence of effectivenes, but which do not recommend themselves for present clinical use. The first of these is adrenal cortical hormone, specifically compound E of Kendall. In accordance with the well known reciprocal relationship between the adrenals and lymphoid tissue,[20] the administration of this compound in very large doses[10] has produced temporary

* Presented at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

regression in mouse lymphoma.

Colchicine is another agent falling in this category. It has both cytotoxic and hemorrhage-producing properties, and has effectively caused regression of certain animal tumors, particularly when implanted under the skin. It was shown by Lits and coworkers[16] to be effective in mouse lymphoma, although regressions were temporary and were succeeded by recurrences of different histopathologic type which were resistant to further treatment. In patients treated with moderate doses (4 milligrams daily by vein) only a transitory reduction in total white blood cell count was observed similar to that seen in normal individuals.[1]

The bacterial polysaccharide from *Serratia marcescens*, which is similar to or identical with the active agent in Coley's mixed toxins, has a deleterious effect on many tumor types, and incidentally on lymphosarcoma. This agent produces very severe systemic reactions and regression of animal tumors associated with hemorrhage and cytotoxic damage. Clinical experience has been relatively disappointing, although regressions of certain human tumors have been observed. Of the first 4 cases of malignant disease treated with this material,[3] one was a patient dying of widely disseminated lymphosarcoma. A single dose of the polysaccharide resulted in an extremely severe toxic reaction (hyperthermia to 107° F. and coma), following which there was virtually complete regression of the tumor masses and relief of other symptoms. After six to eight weeks the tumors recurred and were then resistant to further injections of polysaccharide.

In the case of the three agents mentioned above, the available experimental or clinical evidence suggests that such favorable responses as occur cannot be reproduced, since resistance to their effects is induced almost at once.

Urethane (Ethyl Carbamate). Recent reports indicate that this substance may be effective in causing a reduction in the leukocyte count and considerable palliative effect in human and mouse leukemia.[4,9,17] It has also been partially effective in mammary and prostatic carcinoma.[11,17] It is probably too early to judge the possible usefulness of urethane. The same may be said for stilbamidine, which has been shown to exert a specific action on the malignant plasma cells in multiple myeloma.[21,22]

Radioactive Isotopes. In view of the radiosensitivity of the lymphomas and leukemias, and of the prolonged relief seen in polycythemia rubra vera following total body irradiation, it was natural to anticipate that radioactive isotopes would be of value in these diseases.

Let us consider the characteristics of an isotope which would determine its clinical usefulness. First, it must have an appropriate half-life. Certain isotopes have an extremely short half-life, so that it may be difficult or impossible to remove them from the pile or cyclotron with sufficient activity. Others, with a long half-life and a propensity for deposition in bone or some other organ susceptible to carcinogenesis, will ultimately become very dangerous. There is ample experience to indicate that this is true of radium, and experimental studies have shown that radioactive strontium, plutonium, and other radioactive elements will fall into the same class.[2]

Localization of radiation in the body also conditions the value of an isotope. This is determined by the actual localization of the isotope, and by the range of its radiations. Thus, to cite extreme examples, sodium^{24}, which has an almost uniform distribution throughout the extracellular compartment and an energetic gamma emission, irradiates the body in a manner very similar to that of high voltage total body roentgen radiation. Plutonium, on the other hand, with very discrete tissue localization and a short-range alpha ray, distributes its radiation in a highly non-uniform pattern resulting in extreme exposure of certain cells, relative to the total radiation received by the body.[2]

Radioactive phosphorus (P^{32}) is intermediate between these two in respect to its tissue distribution, since its range is of

the order of 1 millimeter in tissue and it localizes somewhat selectively in bone, hemopoietic and proliferating tissue. Its half-life is 14.6 days. For these reasons it should be expected to irradiate the entire body, but to deliver relatively more ionizing energy to bone marrow, lymphoid tissue, and leukemic cells.[15] Its half-life is not inconveniently short, nor so long as to render chronic irradiation effects a serious hazard

The literature on P^{32} treatment of blood dyscrasias has been reviewed elsewhere.[13] In summary, it has proved extremely valuable in chronic leukemias and usually in lymphosarcomas, of variable usefulness in Hodgkin's disease, and useless in acute leukemias and multiple myeloma. Obviously, its value in Hodgkin's disease may depend on whether the cells of a particular tumor type have a high affinity for P^{32}.

In addition, P^{32} is very valuable in the treatment of polycythemia rubra vera, and has been considered by several investigators to be the treatment of choice in this disease.[13]

Mode of Treatment with Radioactive Phosphorus. The isotope may be given by mouth or by intravenous injection. If given by mouth, care should be taken to promote absorption by administering it two hours before breakfast, and by avoidance during the period of treatment of iron compounds, alumina, milk, and other agents which might hinder the absorption of phosphate. With these precautions, it is usual to assume 75 per cent absorption. Dosage by mouth is therefore one-third greater than by the intravenous route.

Because of body distribution of the radiation, hematologic effects are marked and can be studied by examination of the peripheral blood, which enables one to control treatment. Dosage can be regulated accordingly, although due caution must be used as in the administration of total body roentgen irradiation. In the clinic at the University of Chicago, it has been customary to treat lymphomas and leukemias by the administration of small doses (circa 1 millicurie) once to twice weekly over varying periods, depending upon the response. Polycythemia rubra vera has been treated by a single intravenous administration of 6 to 8 millicuries. As in roentgen therapy, further treatment is determined by the time of recurrence of disease.

It can be calculated that a dose of 6 millicuries to a man of average size (0.1 mc. per kilogram) would, if all retained, deliver in the first day the equivalent of approximately 3 roentgens of total body radiation. Assuming loss of less that 50 per cent by excretion, the total dose would be between 30 and 60 r. Because of the selective distribution of the isotope, the amount of radiation to blood-forming tissues would be somewhat greater.

Nitrogen Mustards. Work done during the war[7] has shown a remarkable parallelism between the effects of these compounds and those of ionizing radiation. One sees destruction of rapidly growing cells and specific damage to hemopoietic tissue. The nitrogen mustards have even been shown to cause genetic mutations and to have a specific inhibitory effect on sulfhydryl enzymes resembling the effects of radiation.[19]

Stimulated by the observed effects of these chemical compounds on the blood-forming tissues, clinical studies initiated by Gilman *et al.*[8] and Jacobson *et al.*[12] have served to add this group to the armamentarium of therapeutic agents in neoplastic and allied hemopoietic diseases. Two nitrogen mustards—methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride—have thus far been given intensive clinical evaluation. These analogous compounds are unstable in aqueous solution and their physiologic action is ascribed to the first transformation product, in which an immonium is formed.[7]

The nitrogen mustards are administered intravenously soon (within five minutes) after they are dissolved in saline solution, by injection into a saline intravenous system already in operation. Thus, thrombosis due to the irritant action of the agent can be avoided, and the substance is introduced before it undergoes chemical changes beyond the production of the effective deri-

vative. In the clinic at the University of Chicago, 0.1 milligram per kilogram of body weight has been given daily over a four to six day period.

Toxic Reactions. The most immediate reaction is nausea and vomiting. This occurs within a few hours after administration and abates three to four hours later. There is considerable variation in the intensity of the reaction, as is true in the case of roentgen sickness. Local thrombosis or phlebitis may be seen at the injection site if the solution has been insufficiently diluted. Severe depression of hemopoietic tissue occurs in both bone marrow and lymphatic tissue, but (unlike, for example, that following benzol) is invariably followed by regeneration.

Therapeutic Results. As with radioactive phosphorus, the nitrogen mustards are ineffective when given in acute lymphatic or acute myelogenous leukemia, or in multiple myeloma. Encouraging results have been seen in chronic lymphatic and myelogenous leukemia, lymphosarcoma, and Hodgkin's disease. In addition, 2 cases of sympathicoblastoma showed marked, though temporary, remissions. Among the chronic leukemias and lymphomas, probably the least satisfactory series of results have been in the chronic myeloid group.

As with radiation therapy of various types, one sees a great diversity of response between patients. It seems clear, however, that the nitrogen mustards have an effect which is often spectacular in terms of disappearance or reduction in size of tumors, especially of lymphatic tissue, and in alleviation of symptoms. It seems equally true that remissions in general, although more complete in the symptomatic sense, are probably shorter than those following roentgen treatment. Similar to roentgen treatment, the nitrogen mustards produce repeated remissions with successive courses of administration, but resistance to treatment eventually develops.

It is noteworthy and encouraging, that certain patients with Hodgkin's disease and lymphosarcoma which have become radiation resistant through protracted roentgen treatment have undergone remissions, sometimes repeatedly, during subsequent nitrogen mustard therapy. Four such cases have been detailed.[12]

In polycythemia rubra vera, results of nitrogen mustard therapy have been favorable as far as can be ascertained at the present time. Because of the long remissions seen in this disease following various other forms of therapy, a proper assay of therapeutic results must necessarily await further experience.

DISCUSSION

Before attempting to assay the comparative value of different agents in the therapy of this group of diseases, it may be well to discuss certain criteria whereby we may attempt to measure them.

The first criterion is localization. On this score roentgen therapy appears to lead the field in the treatment of localized lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease. There is considerable evidence also, of course, indicating that radical local surgery has an important part in the treatment of these specialized situations.[6] Where this is inexpedient, it would appear that a localized lesion can successfully be treated, at least for the purpose of producing a remission, by an amount of roentgen radiation (1,000 or 2,000 roentgens) which could not be tolerated by the whole body. Such localization of the agent to a given segment of the body would not seem possible with such chemotherapeutic agents as the nitrogen mustards.

Another type of localization is that attained by use of the radioactive isotopes. Here we can visualize a situation in which a certain isotope might, by virtue of its chemical or metabolic properties, localize only in those tissues requiring irradiation. In combination with a soft, short range radiation, an ideal set of conditions would be realized. Unfortunately, there is no isotope available for treatment of hemopoietic diseases analogous to radioactive iodine in treatment of the hyperplastic thyroid, where virtually all of the radiation is delivered to the tissue in question. Even if

there were such an isotope with highly specific hemopoietic tissue localization, the radiosensitivity of the normal blood-forming cells would probably limit its value to an extent not encountered in the case of most other tissues.

As we have shown, by virtue of its concentration pattern, radioactive phosphorus is theoretically superior to total body roentgen irradiation in the treatment of polycythemia rubra vera and the leukemias, and also in lymphosarcomas; yet its usefulness is much less in Hodgkin's disease and other tumors which may have no particular tendency to concentrate phosphorus. Little is, of course, known about the localization of most of the chemical agents in neoplastic tissues, although this is probably of equal importance. Colchicine has been found not to concentrate in tumors of mice which are sensitive to it.[1]

A second criterion is the nature of the remission. It seems true that we have no agent which will permanently sterilize leukemia or disseminated lymphoma. All that it is possible to say is that the general nature of remissions after generalized and local radiation and after the use of the nitrogen mustards appear qualitatively similar, with the quantitative differences noted above.

Third, we must consider phenomena such as radiation resistance. It is not our purpose to discuss whether this is due to cell selection, to vascular changes, to gradual impairment of normal hemopoietic function, or to other causes. This only too familiar condition has its parallel in the acquired resistance to nitrogens mustards, and to the other chemical agents for which we have presented clinical or experimental data.

Finally, we need to understand whether the modes of action of agents are different; and hence, whether a second agent may be useful after resistance has developed to a first agent. There is some evidence to suggest that nitrogen mustards may be useful after roentgen-ray resistance has become obvious to the radiologist. It is most important that more information be gained on this point, since, if it is a general truth, combinations of various forms of treatment might represent a considerable advance in therapy. It may be worth while to remember that parallel information about other agents is scanty or lacking.

Thus, although the radioactive and chemotherapeutic agents discussed here may not at the moment show promise of creating a new era, there is still much important work to be done. The nitrogen mustards which have been put to use are only isolated examples of potentially hundreds of analogous drugs which, through different cell localization or diminished toxicity, might prove more effective. The possibility of sensitizing tissue to the action of these agents must also be sought, as well as pharmacologic means of allaying side-effects.

CONCLUSION

A new field is rapidly being opened, both in the use of isotopes and in chemotherapy, which for its growth will require the best we have in clinical observation and in experimental techniques. We may look forward to great efforts on the part of chemists to derive compounds which have effectiveness out of proportion to their toxicity; and on the part of pharmacologists and physiologists to seek the mechanisms responsible for different modes of action and to derive means of allaying side-effects. On behalf of this goal, and in view of the menace of future atomic warfare as well, it will behoove radiologists to pay increasing attention to the hitherto minor problem of radiation sickness, and to the little understood phenomenon of radiation resistance.

950 East 59th St.
Chicago 37, Ill.

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DISCUSSION OF SYMPOSIUM ON RADIOACTIVE ISOTOPES*

Dr. G. Failla, New York, N. Y. This has been a most interesting symposium and I think every speaker should be congratulated for the excellent presentation of the subject he was discussing. In particular, it is rather fine to see that the speakers did not speculate on what can be done with radioactive isotopes in an abstract way but gave us the results of work which has already been done and which has been carefully done.

The publicity we have had about atomic energy has been made up of many speeches indicating in a vague way the great future of radioactive isotopes and how many different things can be done with them. In this Society we want to know exactly what is being done and what has been done, that is much more valuable than any speculation.

As radiologists, a very great opportunity is opening up for all of you, if you take full advantage of it. In order to do this, you will have to study about radioactive isotopes, and you will have to know much more about physiology and the effects of radiation on different tissues than has been necessary in the past.

The complications in the use of radioactive isotopes as therapeutic agents are much greater than in the use of roentgen rays. However radioactive isotopes are here, and will be used and radiologists are the ones that should take the lead in doing this work and doing it safely.

The radiologist is in an excellent position to do that, whereas if we allow others to come into the field who haven't had the background of radiation effects and dangers, there may be a great deal of harm done. That is one of the things that we should emphasize. Great caution has to be exercised because there are dangers to the individual handling the radioactive isotopes

* Papers by Drs. Quimby; Evans; Reinhard; and Brues and Jacobson.

and to the patient, if the proper care is not exercised in the administration of these new agents.

One of the things that is most important is to know where the isotope is going to be deposited in the body, where it is likely to concentrate, because such concentration will be the limiting factor in the dose that can be administered. The material may be rather uniformly distributed throughout the whole body or it may be localized in some particular organ. This information must be known before one can decide how large a dose can be given. Unfortunately, in the treatment of cancer one has to use large tissue doses, as you all know.

In general, one is limited in the application of a therapeutic dose by the tolerance of normal tissues. You have the same trouble with radioactive isotopes. If you know how to protect the patient from the injurious effects of roentgen rays and radium and the limitations of their use, you can carry this knowledge over into the field of isotope therapy and you won't injure anybody—provided, of course, that you know the distribution of the isotope in the body.

Another thing that has been mentioned this afternoon is the question of measurements. There are discrepancies from one laboratory to another. However, these difficulties will be ironed out in the near future. In any case, I would suggest that if you undertake the use of radioactive isotopes you get in contact with a university laboratory in your vicinity where Geiger counters and other measuring devices are available, and get somebody familiar with these instruments to cooperate with you and measure your radioactive isotopes every time before you administer them. The measurements may not be in accord with all the other laboratories, but as far as you are concerned, the main thing is to be able to duplicate your own doses from time to time. In the beginning you will be feeling your way and will start with a low dose; after you have acquired a certain experience, you will probably want to increase that dose. If you know it in terms of your own standard, and your own apparatus, you will be safe, but if you use unchecked measurements made by somebody else, they may vary by a considerable factor and you may do harm.

The physicists will solve the problem of measurements in a much shorter time than the biologist will give you the information about the distribution of isotopes in the body, with respect to the different organs and cellular components, and with respect to time following administration. If you can make your own measurements or get somebody that you know and trust to make them, you can duplicate your treatments with assurance, irrespective of the value of the millicurie or anything else.

Mention has been made about radioactive phosphorus having an ideal half-life for the treatment of leukemia or other therapeutic purposes. I should like to point out that radioactive sodium is probably just as effective in the treatment of leukemia, and that its shorter half-life is advantageous. I think the half-life of phosphorus is perhaps a little too long. If retained in the body P^{32} will produce effects for a considerable period of time, and if by any chance one has administered too much, there is no way of getting it out quickly. On the other hand, if you use radioactive sodium, which has a relatively short half-life of fifteen hours, you can control the dosage better. Some work that has been done with radioactive sodium at Columbia University in the treatment of leukemia indicates that it is equally as effective as phosphorus for that purpose (or equally as effective as roentgen rays).

All leukemia cases, unfortunately, eventually become resistant to any form of treatment and die. That seems to be the case with any one of the agents which has been mentioned today or any agent that has been used in the past. I should like to see some experimental work done to determine why these leukemias become resistant to all sorts of treatment after a certain period of time. Then maybe we can find a real cure for that disease, but that will take time.

As for the dangers to the operator, I think those of you who have used radium, particularly, should know how to protect yourselves from these radioactive isotopes. In any case, one should not expose himself to these radiations for any longer time than is absolutely necessary. Long forceps or long handled devices should be used. Lead screens and protective enclosures should be provided. The objective should be to prevent local overexposure as well as general exposure of the whole body. I am afraid that there will be accidents in spite of all precautions taken, and the more careful you are the better.

DR. L. O. JACOBSON, Chicago, Illinois. In general the remissions produced by the nitrogen mustards are not comparable to those produced by roentgen rays. That is, they are shorter. We have, as Dr. Brues pointed out, treated some patients referred to us by other people as

well as patients from our own clinic who were roentgen-ray resistant. Remissions had been negligible or very brief from roentgen irradiation and we have produced remissions of six months and more with mustards on repeated occasions.

I also want to say a word about the toxicity of radiations or chemical substances in the treatment of these dyscrasias. We are frequently too alarmed by the leukopenias that occur after such treatment. I don't want to leave the impression here today, however, that we should pay no attention to the development of leukopenia, but in the past four years in which we have used the nitrogen mustards, we have seen many leukopenias below a thousand on many occasions without any untoward effects. In one case an erysipelas developed. The erysipelas was treated satisfactorily with penicillin.

Maybe we have been lucky, and the next ten cases will get infection if we do treat with doses of nitrogen mustard large enough to produce severe leukopenias. This seems unlikely in our experience.

As far as penetrating radiations and radioactive materials are concerned, experience on the Plutonium Project tends to indicate that the leukopenia is only one manifestation of pathological effects and per se is probably not the most serious.

The question has come up during the treatment of patients with the nitrogen mustards, whether or not one might be able to double the dose? For example, of a dose of 25 milligrams of mustard produces a leukopenia of less than a thousand, could you give 50 milligrams and therefore get more effective remissions? We have tried this but as yet have no good evidence that remissions thus produced are longer or more complete.

I want to bring up one question for Dr. Reinhard, Dr. Evans, and others. Polycythemia has been treated in the past with cathode roentgen rays, with P^{32}, and now lately with mustard. Our results with the mustards have been quite interesting. We still have, after a period of from six months to twenty-four months, 6 patients in remission that were treated with the nitrogen mustards. With roentgen therapy, remissions in our experience, at least, have been relatively short. The remission is longer with the P^{32} than it is with roentgen rays even though the degree of effect on the peripheral blood and the bone marrow are comparable in terms of the leukopenia, and so forth. Is this due to the fact that the half-life of phosphorus is 14.3 days and therefore the effect is over a longer period? Or is it due to some other mechanism?

Dr. Paul S. Henshaw, Oak Ridge, Tenn. We have heard this afternoon a series of very interesting and stimulating papers dealing with radioactive isotopes. We have heard of both the successful attempts, to use these new agents, and of unsuccessful attempts.

Since no issues have been raised, however, with which I am competent to deal, I will not attempt to discuss any of the papers. However, since I am now associated with the radiobiologic work at Oak Ridge, perhaps it would be in order to mention very briefly something about the availability of isotopes.

Dr. Paul Aebersold, whom you know, and who is at this meeting today, is in charge of the distribution of isotopes from Oak Ridge. He has associated with him an advisory staff and a group of associates to carry on the work. It is not my purpose to speak for him, but perhaps I am in a position better than he to say that this group has spent a great deal of time in making preparations for the distribution of isotopes.

It was necessary for them, first of all, to arrange a catalogue of available materials and the amounts. Next it was necessary to find feasible ways of shipping these materials. It was necessary also to arrange to separate the isotope work from the atomic bomb work, so that the secrecy provisions were not an obstacle in distribution.

Perhaps the greatest service that this group is now able to render is that of advising prospective users of such materials as to whether it will be possible or feasible to undertake the work they have in mind. This staff will examine the proposals and ask questions as to whether proper detecting and measuring instruments are available, whether proper protective measures are in use and so on.

They will even inquire as to whether the proposed problem has been properly conceived and they will make suggestions as to the prospects of getting answers to the questions raised.

I think I may say for Dr. Aebersold that he will be glad to receive requests for information or requests for the use of isotopes at any time from any of you.

Dr. H. J. Ullmann, Santa Barbara, California. Dr. Jacobson spoke of radiation sickness occurring during the treatment of leukemias with the roentgen ray. I believe it entirely un-

necessary to produce roentgen sickness, and that it only occurs with gross overdosage. I can see no valid reason for such large doses when one can get satisfactory remissions with a dose of 50 to 100 r measured on the skin. I treat once a day but not until I have the white count, taken shortly before treatment. This daily dose is continued until there is a daily progressive fall in the total white count. It is then discontinued until the count ceases to fall. Some patients will go along with a falling count for several weeks after the last treatment and obviously should have no further irradiation. Treatment is not resumed unless the fall stops before a satisfactory count is reached or begins to rise. But treatment is never based on count alone. All clinical factors must be taken into consideration. No roentgen sickness is ever produced by this method. I brought this up to get it on the record, because I have heard "roentgen sickness" employed so much as an argument against the use of the roentgen ray in the treatment of the leukemias. The production of roentgen sickness is absolutely unnecessary.

DR. G. FAILLA, New York, N. Y. I would like to ask Dr. Brues and Dr. Jacobson whether they have used the two agents in combination—the phosphorus and mustards?

DR. L. O. JACOBSON, Chicago, Illinois. We have studied some of these patients with repeated courses of nitrogen mustards for long enough periods to give us a fair approximation of the expected remission. We have alternated mustard treatment with roentgen threrapy. We have combined mustard therapy with roentgen therapy. In general, alternating nitrogen mustards with roentgen therapy does not seem to be any more effective than treatment with one or the other alone. We have combined mustard therapy with simultaneous therapeutic doses of P^{32}. This procedure failed to produce longer or more satisfactory remissions. On the other hand, treatment with nitrogen mustard and simultaneous treatment with roentgen therapy has proved to be quite effective. This latter procedure combines general therapy with local therapy.

DR. EVANS (closing). I would like to emphasize that the local concentration C may vary from point to point in a tissue mass. Then the local dosage will vary in proportion. If the average range in tissue of the particular beta rays involved is l, then C is to be interpreted as the local concentration in volume elements of the order of l^3. This will amount to 1 or a few cubic millimeters in most cases. The dosage throughout a large tissue mass can be taken as uniform only if it is known that the concentration of the isotope per $mm.^3$ is substantially constant throughout the tissue mass.

DR. REINHARD (closing). Dr. Jacobson raised the question as to why remissions obtained in polycythemia with radioactive phosphorus are longer than with roentgen irradiation. I don't know whether they are longer or not. I am not sure that there are sufficient data now available to determine whether or not remission with radioactive phosphorus is longer than remission obtained from roentgen irradiation.

I think probably if the remissions are longer, one reason may be that at first the correct dosage of radioactive phosphorus was not known. We have been using this agent for a relatively few years and certainly a good many patients who received radioactive phosphorus were overtreated. If you give enough radioactive phosphorus to push the erythrocyte count down to 3,000,000, certainly the remission is going to last a little longer than if you give just enough to bring it down to 5,000,000. If you were to give comparable amounts of radioactive phosphorus and roentgen rays in terms of radiation delivered to the bone marrow to two groups of patients with polycythemia, I doubt whether there would be any difference in the duration of remission

Dr. Ullmann raised the question of radiation sickness. I made that statement and not Dr. Jacobson. I think if I may quote the statement, no one can object to it. I made the statement that freedom from radiation sickness is one *possible* advantage of radioactive phosphorus.

I am aware that there are methods of giving roentgen therapy which obviate the difficulty of radiation sickness. However, as roentgen therapy is ordinarily given, radiation sickness is sometimes seen. I was merely trying to emphasize the fact that radiophosphorus gives the ultimate in low grade radiation over a long period of time.

There is no practical means of giving roentgen therapy in such a manner as to obtain very low grade radiation continually over a period of days or weeks.

Vol. 58, No. 6

ANALYSIS OF TECHNICAL FACTORS AND RESULTS OF TREATMENT IN CARCINOMA OF THE CERVIX UTERI

DESCRIPTION OF IMPROVED RADIUM APPLICATOR

By G. E. RICHARDS, M.D., LL.D., F.R.C.P.(CAN), F.A.C.R.
Ontario Institute of Radiotherapy, Toronto General Hospital
TORONTO, CANADA

SEVERAL recent writers on the subject of the treatment of carcinoma of the cervix uteri have expressed the opinion that radiotherapy is now static, that little more may be expected from it and have suggested as an alternative a return to surgical methods at least for certain selected cases. In a paper by Meigs[2] on this subject the statement is made that "the treatment of cancer of the cervix by radiation is at a standstill", and he quotes with approval a paragraph from Miller of the University of Michigan Hospital as follows:

> The limitations of existing methods of treatment are well recognized. No one expects the impossible, but there is good reason to believe that therapy is disappointing. We appear to have reached that comfortable state wherein we hesitate to disturb the efficiency of a therapeutic system which has taken a long time to establish. Perhaps the ease of administration, as well as the apparent effectiveness of irradiation therapy, has lulled us into a state of inertia, in which we fail to exploit existing methods of treatment to their fullest capacity. In radical abdominal hysterectomy, as first performed by W. A. Freund in 1878, and later popularized by Wertheim, was recognized a potent weapon for combatting cervix cancer. But because of its high primary operative mortality rate, and its restricted field of usefulness, the operation was permitted to pass into the discard. Radium and X-ray have also proved their worth. Yet, after almost a quarter century devoted to the refinement of technic and stabilization of procedure, I find there is little to boast about. . . . Perhaps we have reached the end of an era.

These and other somewhat similar statements are sufficiently challenging to cause us to carefully review the whole subject and to inquire whether this pessimistic outlook is justified by the facts. The present paper will, therefore, be devoted to an inquiry into three questions:

(1) How do the best results obtainable by surgery compare with the best results by radiotherapy?
(2) Is progress still being made in radiotherapy or is it a fact that the latter is "at a standstill"?
(3) Can further improvements be expected in radiotherapy in the future?

(1) *Comparison with Results by Surgery.* It has been stated by many writers that it is difficult and inaccurate to compare the results of treatment by surgical methods with those obtained by radiotherapy. And yet no very convincing reasons are brought forth in defense of this position. The work of Bonney in England and of Taussig in America are commonly cited as examples of the best results obtainable by radical surgery. Bonney[1] operated upon 500 patients out of a total of approximately 900 actually diagnosed as cancer of the cervix. His five year cure rate is stated to have been 40 per cent for those in whom no glandular extension had occurred and 22 per cent for those in whom lymph node involvement was present—in other words, 40 per cent for those cases which now would be classified as Stage I and II; 22 per cent for *operable* Stage III. *All* Stage IV and the *majority* of Stage III cases were excluded since they were considered inoperable and do not appear in the statistical report. Thus the five year figures refer strictly to patients operated upon, not to the percentage of all cases seen as is the general rule in radiological reports. If the figures

* Presented at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

quoted took into consideration all cases diagnosed as cancer as well as those operated upon, it is clear that the five year survival rate quoted would need to be substantially reduced and would be closer to 25 per cent for the first group and 15 per cent for the second. Taussig is reported to have operated upon 70 patients in Stage II with a five year survival rate of 37 per cent.

So far as actual "cure" by surgery is concerned it may be assumed that these figures represent, if not the best attainable, at any rate the best that have been attained up to the present. For comparison with radiotherapy it is important that they be compared with work of an equally high standard representing modern techniques, whereas quite frequently when such a comparison is undertaken by a surgeon figures are selected which do not at all represent the best that radiotherapy can be expected to accomplish. For example, in the paper already quoted, speaking of Taussig's operative results, Meigs says: "Of 70 patients in Class II of the League of Nations Classification 37 per cent were living and well after five years. In a parallel group of 118 patients treated by radiation alone the five year salvage was only 23 per cent." It we are to understand a "parallel group" to mean Stage II of the League of Nations classification the figure quoted (23 per cent) certainly does not represent the results at present being obtained in modern radiotherapy clinics, and in the interests of an accurate estimate it is important that this fact be taken into consideration. Many such series of figures are available in the literature. The figures used in the present paper for illustration are taken from the recently issued report from Manchester shows five year net survivals (for the year 1938) as follows: Stage I, 71 per cent; Stage II, 52 per cent; Stage III, 37 per cent. Thus, the average of Stages I and II which may be compared with Bonney's cases without lymph node invasion is 61 per cent against Bonney's 40 per cent; and those in Stage III with lymph node involvement 37 per cent against Bonney's 22 per cent. Taussig's figure of 37 per cent would have to be compared with the Manchester figure for Stage II of 52 per cent. I do not see how one can escape the conclusion that this comparison is fair and accurate. Furthermore, these facts refute the statement that radiotherapy is incapable of controlling lymph node invasion since this type of invasion must necessarily be present in all Stage III cases in which, as has been shown, the five year survivals amounted to 37 per cent.

TABLE I

CARCINOMA OF THE CERVIX UTERI, 1929–1940

(Gross survivals—no deductions)

Stage	Number of Cases	Living at end of—		
		3 years per cent	5 years per cent	10 years per cent
I	92	80.8	74.0	50.5
II	277	62.5	50.5	29.03
III	335	33.5	26.8	13.6
Total I, II and III	704	51.3	42.5	26.25
Stage IV	158	11.4	4.9	0
Total—all Stages	862	43.9	35.6	21.9

Results in this Institute. Since 1929 we have treated in this Institute 1,142 cases of

cancer of the cervix of which three year figures are available in 862 and five year figures in 669 and ten year survivals in 333 cases. These results are shown in Table I indicating that results of the order of those quoted from Manchester are not unusual and are no doubt being obtained in most well organized radiotherapy centers.

Thus the first conclusion to be reached is that radiotherapy is still superior to surgery by a substantial margin in those cases in which surgery is possible and has a very useful place in many cases in which surgery is quite impossible. In 57 cases operated upon by Meigs, injury to the ureters occurred in 10 per cent. One may be quite certain that if any such percentage of serious injuries occurred as a result of radiation therapy the method would be roundly condemned by nearly all surgeons. No one will criticize Meigs and a few other surgeons of like caliber in making an effort to equal or better Bonney's work. But it would be a definitely retrograde step if throughout the country the teaching were adopted that cancer of the cervix should again be treated surgically. There are too few Bonneys and Taussigs for such a procedure to have any other result except a general reduction in the cure rate now being secured in this type of cancer.

(2) The second question in which we are interested is whether "the treatment of cancer of the cervix by radiation is at a standstill".

A correct answer to this question should be equally interesting to gynecological surgeons and to radiotherapists and is certainly vital to the patient.

Table III includes a tabulation quoted in full from Meigs' article partly because it is an excellent compilation of figures from nine large clinics, both in Europe and America, but also because most readers will recognize the figures as being about fifteen years old and therefore as forming a suitable group for comparison with more recent work. Below Table III have been added more recent figures from several centers representing present methods and results. On this basis, it is apparent that quite substantial progress has been made in all groups except Stage IV. That an equally substantial improvement in the general average has not occurred may be explained by the fact that there is a widespread tendency to refer late cases to radiotherapy centers for the purpose of receiving palliative treatment and nursing care and the statistical tables are heavily and unfavorably weighted with such cases as a result. It is apparent, in spite of this, that defi-

TABLE II

CARCINOMA OF THE CERVIX UTERI

Comparison of Results by Surgery and Radiotherapy

		Stage I and II		Stage III	
SURGERY		No. cases	5 year per cent	No. cases	5 year per cent
	Bonney	500	40		22
	Taussig	70	37		
RADIOTHERAPY	Average of 9 clinics	2233	45.7	2417	21.2
	Manchester 1934–38	340	53.5	241	27.0
	1938 only	70	61.0	53	37.0
	Toronto 1929–40	289	62.2	257	26.8

nitely favorable progress has been made. The figures quoted would indicate an improvement up to 1938–1940 of the order of 20 per cent in Stage I, 15 per cent in Stage II, 5–6 per cent in Stage III and little or no change in Stage IV.

(3) By far the most important question to the radiotherapist, however, is the last, namely—Can further improvements be looked for in the future, or have we, as Miller suggested, reached the end of an era? We believe that answer is in the affirmative and that such improvements are

TABLE III

ANALYSIS OF RESULTS OF TREATMENT FOR CARCINOMA OF THE CERVIX

Institution	Stage I		Stage II		Stage III		Stage IV		All Stages	
	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured
Memorial Hospital (New York City)	17	52.9	15	46.7	74	18.9	30	10.0	136	24.3
Women's Hospital (New York City)	9	55.5	24	25.0	18	16.7			51	27.3
University of Brussels (Brussels)	6	33.3	20	40.0	28	14.3	9	0.0	63	22.2
Liverpool Radium Institute (Liverpool)	8	62.5	28	25.0	43	14.0	15	0.0	94	19.1
Marie Curie Institute (Paris)	9	66.6	20	60.0	75	20.7	22	4.5	126	33.3
Radium Center (London)	4	25.0	27	11.1	37	18.9	19	0.0	87	12.6
Institut du Cancer (Paris)	9	44.4	15	53.3	40	35.0	19	10.5	83	33.7
Institut du Radium (Paris)	12	66.6	44	43.2	34	32.3	12	8.3	102	38.2
Radiumhemmet (Stockholm)	31	48.4	67	26.9	71	8.5	42	9.5	211	20.4
All reporting hospitals	607	55.2	1,626	36.3	2,417	21.2	1,020	5.3	5,670	26.3
Recent Figures										
Marie Curie Hospital (London)—1945 Report	88	76.1	377	58.6	734	29.4	211	7.6	1,410	36.9
Manchester—1945 Report (1934–1938)	48	65.0	292	42.0	241	27.0	245	6.0	826	28.0
Toronto—1945 Report (1929–1940)	73	74.0	216	50.5	257	26.8	123	4.9	669	35.6

to be found in three directions: (1) by a more careful application of physical principles and dosage factors now well understood; (2) by an improvement in the technical details of applying radium and its more skillful combination with roentgen therapy since in all cases except a relatively few both methods are essential, and (3) in the full utilization of the newer radioactive materials which will shortly be available and which give at least the promise of solving the problem of providing adequate dosage throughout all parts of the pelvis.

Physical Principles Underlying Treatment. Sufficient work has now been done, both experimental and clinical, to permit us to apply the basic physical principles to the problem of cervical carcinoma far more accurately than at any time heretofore. The essential factors may be recapitulated as follows: A satisfactory technique must be one which delivers a lethal dose throughout the cervical and pericervical tissues and if possible, to the side wall of the pelvis. This lethal dose must be so distributed and timed as to avoid injury to small intestine, bladder, rectum, ureters or sigmoid. Calculations of "tumor doses" to be acceptable according to present-day standards must be much more accurate and precise than can be expressed by simply stating the dosage delivered to each skin portal.

Tod and Meredith[5] called attention in 1938 to the fact that the most sensitive area in the pelvis is the point at which the uterine artery crosses the ureter since at this point there is located a lymph node (the obturator node) and excessive doses here will result in injury to the ureter which may produce strictures of various degrees of seriousness. They therefore called this critical area Point A and described it as lying 2 cm. lateral to the internal cervical

orifice and 2 cm. anterior to the plane of the cervix. They also described a point 5 cm. lateral to the midline of the cervical canal as Point B, and Neary[3] has indicated the rectovaginal septum as Point S. According to their technique dosage delivered at Point A should not exceed 7,500 r and at Point S must not exceed 5,000 r.

Several years ago we adopted these general principles and have slightly modified them in the following manner:

In order to accurately plot the dosage for the individual patient a roentgenogram of the pelvis is taken as in obstetrical pelvimetry and from this roentgenogram accurate measurements are made. A contour drawing of the patient is then prepared in the conventional manner corrected by means of calipers and transferred to tracing paper. On this contour drawing a tracing of the bony pelvis is made using the measurements obtained from the roentgenogram which tracing now represents an outline of the patient's pelvis with an accuracy of ±0.5 cm. From prepared transparencies the position of the uterus and vaginal vault are added to the tracing and Points A, B and S established. The tracing now permits one additional point to be determined, namely the true position of the wall of the pelvis and this we have designated Point C. The above points are clearly shown in Figure 1. For full discussion of the physical factors involved the reader is referred to Neary's excellent article on this subject.[3]

Since most of the lymph nodes in the pelvis lie close to the pelvic wall it is essential that a dose lethal for carcinoma be delivered at Point C and this dose should be 5,000 r or higher. Numerous studies by many workers have demonstrated that this is not possible by means of radium alone in the form commonly employed and not possible by roentgen therapy alone, short of excessive skin doses. The problem is, however, capable of solution by a combination of both, and a satisfactory technique should be one, in our opinion, which provides for the most effective possible combination of these two forms of radiation since we are concerned with "radiation" therapy in the broad sense and not with either "roentgen" or "radium" therapy as such.

The first question which arises is: "Which is the most desirable order?" We believe there are numerous reasons why roentgen therapy should precede radium:

1. At the end of a course of roentgen therapy the bulky tumor originally present will usually have either completely disappeared or at least will have undergone very marked regression, ulceration will have healed and with it secondary infection will have disappeared, thus greatly simplifying the application of radium and reducing its dangers. In a previous publication from this Institute[4] it has been reported that prior to the introduction of preliminary roentgen therapy 12 per cent of all mortality and 16 per cent of all morbidity were due to the presence of infection. Since the use of preliminary roentgen therapy the complications due to infection have been greatly reduced and with the introduction of penicillin and the sulfonamides this no longer presents a serious problem.

2. The preliminary roentgen series is a very good therapeutic test for radiosensitivity of the particular neoplasm with which one is confronted. If no improvement is secured following an adequate roentgen series the tumor is usually highly resistant and will require the highest possible dosage or may indeed be incurable by radiotherapy.

We are therefore of the opinion that the roentgen series should precede radium in all cases except Stage I and certain Stage II cases in which there is no serious objection to completing the radium series first.

Roentgen Therapy. In patients who weigh only 110–115 pounds it probably does not greatly matter whether this treatment is carried out at 200 kv. or higher, but above 115 pounds and certainly above 125 pounds there is no doubt that a great advantage is derived from the use of higher voltages. In our Institute this treatment is carried out at 400 kv., using a distance of 100 cm. and a filter equivalent to 6 mm. Cu. The half-

value layer is 4.5 mm. Cu, and the depth dose at 10 cm. 37 per cent.

A very few cases in which calculations are made using four, five or six portals provide convincing evidence that six portals are almost essential for adequate rotation, one portal per day. The posterior portals are directed obliquely leaving a wide central space so as to avoid the rectum.

By referring to Table IV it will be seen that in a patient weighing 135 pounds, if

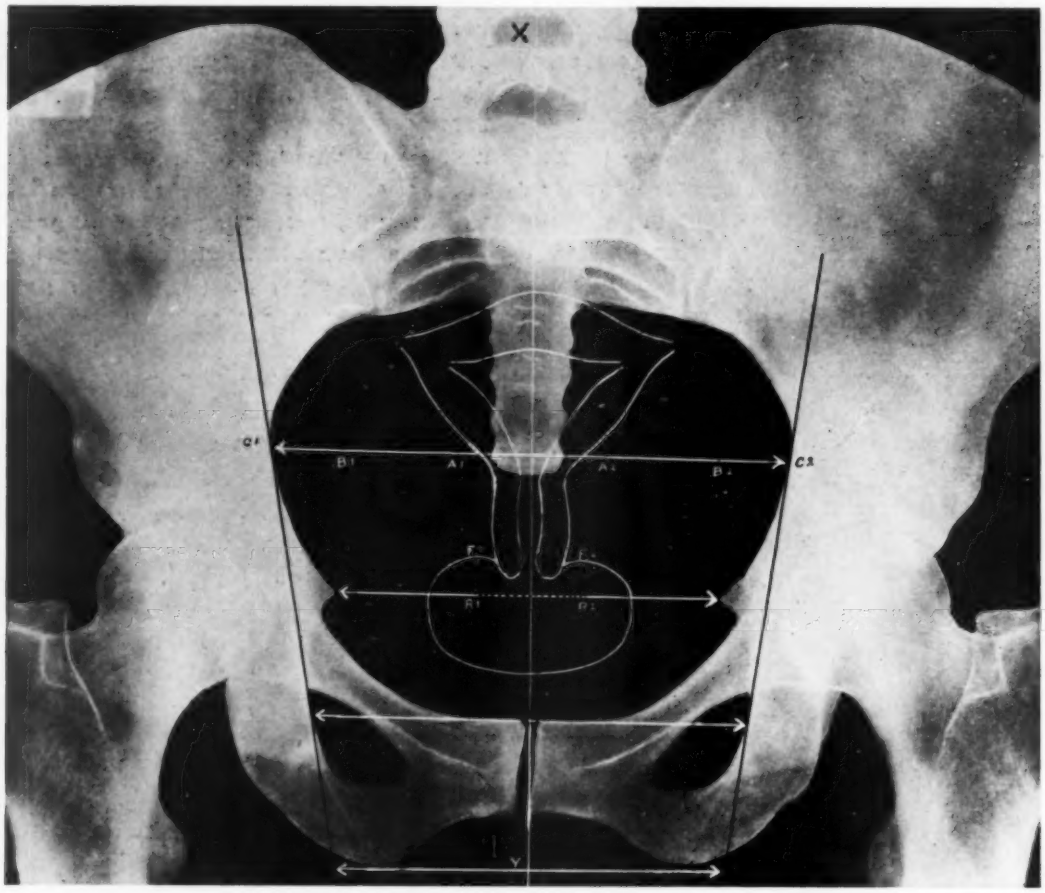

FIG. 1. Showing position of radium sources in vaginal vault designated R_1, R_2; also Points A, B and C, as described in text.

therapy, two anterior, two posterior, and right and left lateral. This becomes a time-consuming procedure and in order to minimize time and permit the completion of each "cycle" in a working week of five days, we have found a double or "twin cone," as shown in Figure 2, very convenient. This cone is used with as much compression as the patient can tolerate for the anterior portals only and these two 10 by 15 cm. portals are delivered simultaneously at one sitting, the other portals being treated in the total dose per portal is 1,800 r, the amount which can be delivered at Point C will be 3,150 r. If the dose per portal is carried to 2,400 r the amount delivered at Point C will be 4,190 r. Heavier doses than these will frequently cause undesirably severe skin reactions or the complication of cystitis or proctitis. A very good combination has been found to be 1,800 r on the anterior and posterior portals while the lateral portals are carried up to 2,400 r or higher, the object of this procedure being

to hold back the dosage at Point A (since this can always be carried to any point desired by means of the radium application) and build up the dosage reaching Point C to the highest level the tissues will tolerate.

If, instead of the six portal technique five portals are used, the dose delivered at Point C will be 2,380 r, while if only four portals are used this dose will be further reduced to 2,090 r. Calculations in these tables are prepared from standard isodose and depth dose charts. Therefore, both from the standpoint of total dosage and of better distribution the six portal method seems to offer many advantages. The details are tabulated in Table IV.

Interval Between Roentgen and Radium Therapy. As has been previously stated the objective in the administration of the roentgen therapy is to secure as high a dosage at Points B and C as possible with a minimum of injury to sensitive structures. Treatment will be discontinued for any one of the following reasons: (1) the required dosage has been reached; (2) a severe skin reaction is developing which it is undesirable to carry further; (3) proctitis or cystitis is developing of such intensity as to preclude carrying treatment further.

In the presence of either of the two latter it is essential to allow the tissues an interval to recover before proceeding with the radium series. Even if these complications are not present it is important to permit the full biological effect of the roentgen therapy to be reached before proceeding with the radium therapy. The optimum time in our experience is three to four weeks, by which time the tumor cells have undergone very considerable regression, and radium, if applied at this stage, is highly cumulative in its effect so that an effective dose may be delivered with greater certainty than if radium is applied as the first procedure to a

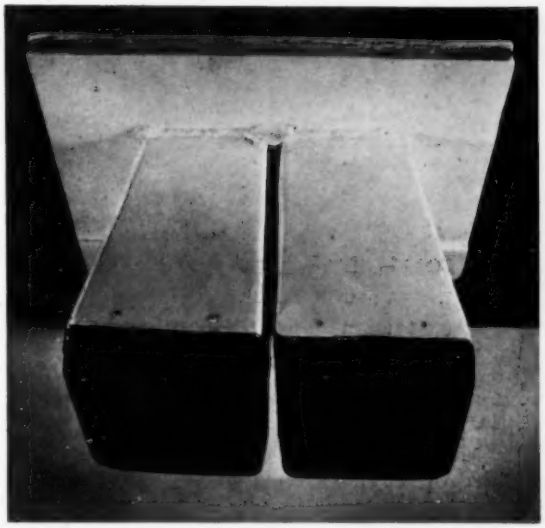

Fig. 2 "Twin cone" by means of which the two anterior portals are treated simultaneously.

Table IV

DOSAGE DELIVERED BY ROENTGEN THERAPY

No. of Portals	Dosage in Roentgens (in air) per Portal	Point A	Point B	Point C	Point S
4	1,800	2,090	2,050	2,090	1,210
4	2,100	2,430	2,380	2,430	1,410
4	2,400	2,780	2,720	2,780	1,610
5	1,800	2,860	2,580	2,380	2,640
5	2,100	3,330	3,000	2,760	3,070
5	2,400	3,810	3,430	3,160	3,520
6	1,800	2,970	2,970	3,150	1,870
6	2,100	3,460	3,460	3,660	2,180
6	2,400	3,960	3,960	4,190	2,490

bulky, secondarily infected and actively growing neoplasm. If an interval of longer than three or four weeks is permitted several dangers may be encountered:

(1) The maximum degree of regression may have passed and when the radium series is carried out it is applied to a neoplasm already recovering from the effect of the roentgen therapy and again growing rapidly, obviously a most undesirable development to permit.

(2) By reason of the healing of ulceration the tissues about the vaginal vault may undergo too great contracture, thus making the insertion of suitable radium applicators much more difficult or indeed impossible.

(3) Similar contracture may occur in the cervical canal. If the interval is too long the canal may become completely stenosed so that it cannot be located or, if located, cannot be dilated, thus making the intrauterine and intracervical application of radium impossible.

Thus, every effort is made to ensure the carrying out of the radium series in not less than three weeks, and preferably not more than four weeks, following the completion of the roentgen therapy. This rule is departed from only if proctitis or cystitis still persists from the previous therapy.

Radium Therapy. In the past there have been several objections to the type of applicators available for the treatment of cervical carcinoma:

(1) *Inflexibility:* This criticism would be applied to metal applicators in which the intrauterine and vaginal radium are combined, i.e. most T-shaped applicators.

(2) *Insecurity:* This is a very serious criticism and applies to corks, colpostats, boxes and almost all multiple applicators held in place by packing. A roentgenogram taken a few hours after the insertion of such applicators is usually very disillusioning if one is greatly concerned about accuracy.

(3) *Danger to Personnel in Handling:* Very few applicators at present in use have been so designed that all handling during loading and most of the manipulation in placing the applicator in position during treatment may be done by means of forceps.

Description of New Type Radium Applicator. In an attempt to overcome some or all of these objections we have designed an applicator which we believe has certain advantages. It consists of two end-pieces, in which the radium is loaded, which are separated from each other by a bridge or spacer. The end-pieces follow the design originally described by Paterson and Parker and conform to the shape of the field of intensity around any radium source. Originally, these were in the form of hollow shells of spun brass, chromium plated, and in the center of each is a platinum-iridium tube of 0.5 mm. wall thickness. This tube may be made of any size or thickness to carry any radium loading which may be decided upon. A cover is provided which is hinged at the mid-point of the bridge so that in loading it can be raised and lowered entirely by instruments. The entire applicator when ready for use is enclosed in a rubber "jacket". The most recent model of this applicator is made of nylon which entirely eliminates all metal parts, is strong and rugged in use and may be sterilized by boiling. Nylon has a molecule composed of carbon, hydrogen and nitrogen all elements having the same atomic numbers as tissue and being free from impurities of high atomic numbers such as frequently occur in rubber.

The bridge or spacer is provided with apertures into which a "fork" is fitted during the manipulation of placing the applicator in position against the cervix. Once in place the applicator is under complete control of the operator and may be placed and held in any position desired. Light packing is inserted merely for the purpose of keeping the tissues out of contact with the instrument. The distal end of the controlling "fork" protrudes from the vaginal orifice and is fastened to a belt which the patient wears throughout the treatment. (A self-retaining catheter is inserted before the belt is finally adjusted and suitable pads are used for protection.)

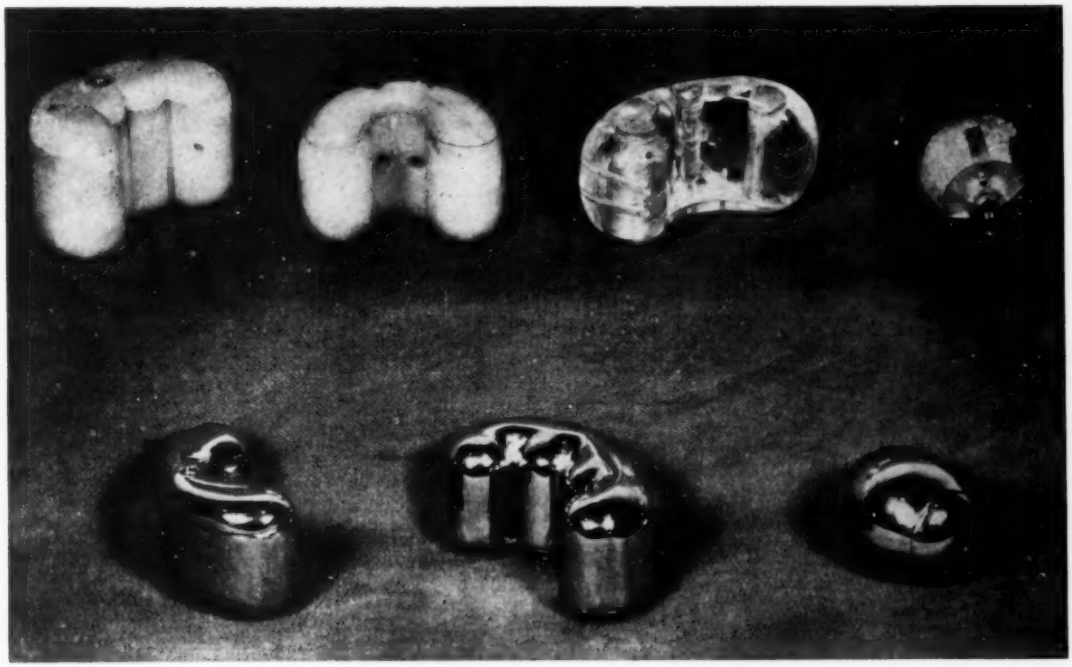

Fig. 3. Top row, four sizes of applicators made of nylon as described in text. Bottom row, metal applicators, spun brass, chromium plated.

Once in place this applicator cannot slip from the position in which it is placed in any direction whatever, either towards either side or, perhaps even more important, cannot either tip over facing the bladder and rectum (which is without doubt the most common cause of cystitis, proctitis and rectovaginal complications), or be partially expelled. Four sizes of the applicator are available and provide amply for the requirements of individual selection (see Fig. 3 and 4).

Protection of the Rectum. In the past, one of the most troublesome complications in the treatment of cervical carcinoma has been due to proctitis either during or following the completion of therapy. Measurements made with conventional applicators show that in most cases in which adequate dosage has been delivered to Points A, B and C, the dosage reaching the rectovaginal septum, Point S, has usually been above 5,000 r which is about the tolerance limit of the rectal mucosa. In the applicator here described the rectum is protected by means of a special built-in filter. In the present applicator the material used for this filter is either gold, platinum or lead, but in the future, as suggested by Mayneord, metallic uranium will be used for this purpose. Owing to its very high atomic weight it is

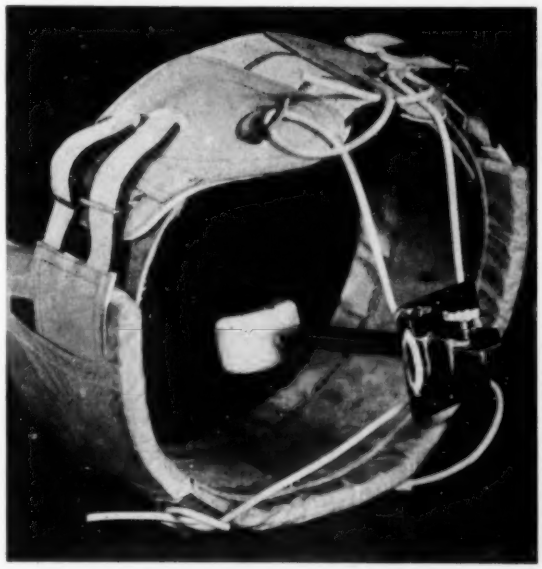

Fig. 4. Applicator ready for use showing "fork" and method of attaching to belt.

especially suitable for this purpose. By this means the intensity of radiation reaching Point S can be reduced 25–30 per cent or even more if desired, thus permitting the use of as high dosages in the parametrium as these tissues will tolerate.

The intrauterine applicator is a simple tandem in rubber tubing as, in our experience, this, by reason of its greater flexibility, tends to ease of insertion.

Dosage. The dosage in each individual case is determined by a calculation (with apologies to all physicists) which takes into consideration the dose which has already been delivered by means of roentgen therapy.

If the plan of treatment has all been charted prior to the commencement of the roentgen series, the dosage of radium required will be known and will be the amount required to build up the dosage at each of the specified points (A, B and C) to that which is lethal for cancer or to the tolerance limit of tissues at each of these points and will usually be the latter. Some indication as to the degree to which the individual tumor may be expected to respond will have been gained during the roentgen series or at least prior to the administration of the radium, and this will influence the loading of the radium applicators as well as the total dose delivered. In an average case the intrauterine tandem would carry 40 mg. enclosed in 1 mm. platinum filter, while the vaginal applicator already described would be loaded with 30 mg. in each end and having a filter of 1.5 mm. platinum. Under these conditions 3,500 mg-hr. will be delivered in $87\frac{1}{2}$ hours. Thus the decision to be made is whether this is sufficient or whether either the roentgen dose should be increased or that of the radium. Having reached this decision it would be modified in actual practice only in case the patient fails to tolerate the roentgen therapy well.

TABLE V

DOSAGE DELIVERED BY RADIUM THERAPY

Type of Applicator	No. of Milligram-Hours	Point A	Point B	Point C	Point S
Intrauterine tandem (40 mg.)	3,000	3,690	780	420	250
	4,000	4,920	1,040	560	320
	4,200	5,170	1,100	590	350
	5,000	6,150	1,300	700	400
Intravaginal (2×30 mg.)	3,000	1,050	570	360	1,800
	4,000	1,400	760	480	2,400
	4,200	1,470	800	500	2,500
	5,000	1,750	950	600	3,000

In the case previously quoted by way of illustration the conditions are as follows:

(1) A roentgen series using six cycles as previously described together with a radium dose as above will give at Point A, 8,535 r; Point B, 4,730 r; Point C, 4,210 r.

(2) A roentgen series using eight cycles with the same radium dosage will give: At Point A, 8,700 r; Point B, 5,310 4; Point C, 4,970 r.

If there is evidence that the tumor is resistant and heavier doses are required this would usually be accomplished by increasing the radium to 4,200 mg-hr. which would result in the following: At Point A, 10,600 r; Point B, 5,860 r; Point C, 5,280 r.

This is a very high dose at Point A and should only be undertaken with great caution and such a dose should always be

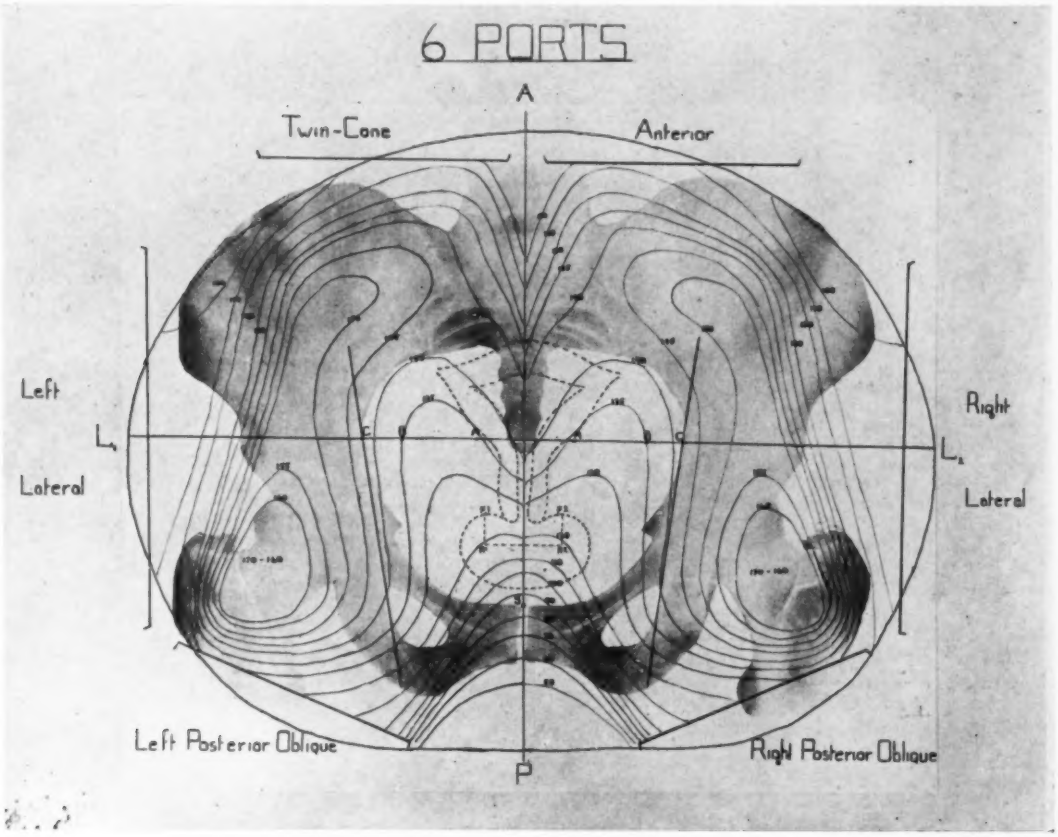

FIG. 5. Isodose chart combining roentgen and radium series.

TABLE VI

DOSAGE DELIVERED BY RADIUM SOURCES R_1, R_2, R_3, IN r PER HOUR

	1 mm. Pt filtration of each source					1.5 mm. Pt filtration of each source					2.0 mm. Pt filtration of each source				
No. of mg. in each source	100	200	300	400	500	100	200	300	400	500	100	200	300	400	500
A	145	290	435	580	725	133	266	399	532	665	118	236	354	472	590
B	68	136	204	272	340	62	124	186	248	310	56	112	168	224	280
C	52	104	156	208	260	44	88	132	176	220	40	80	120	160	200
S	155	310	465	620	775	142	284	426	568	710	127	254	381	508	635

TOTAL DOSAGE DELIVERED IN r BY RADIUM SOURCES R_1, R_2, R_3

	1 mm. Pt filtration of each source					1.5 mm. Pt filtration of each source					2.0 mm. Pt filtration of each source				
No. of mg-hr. in each source	2,000	4,000	6,000	8,000	10,000	2,000	4,000	6,000	8,000	10,000	2,000	4,000	6,000	8,000	10,000
A	2,900	5,800	8,700	11,600	14,500	2,660	5,320	7,980	10,640	13,300	2,360	4,720	7,080	9,440	11,800
B	1,360	2,720	4,080	5,440	6,800	1,240	2,480	3,720	4,960	6,200	1,120	2,240	3,360	4,480	5,600
C	1,040	2,080	3,120	4,160	5,200	880	1,760	2,640	3,520	4,400	800	1,600	2,400	3,200	4,000
S	3,100	6,200	9,300	12,400	15,500	2,840	5,680	8,520	11,360	14,200	2,540	5,080	7,620	10,160	12,700

The addition of protective filter as described in the article reduces dosage at Point S (rectovaginal septum) 25–30 per cent.

SUMMARY OF HISTORY AND TREATMENT

NAME: Doe, Mrs. John

DIAGNOSIS: February 15, 1939, Carcinoma of Cervix, Stage III.

PATH. REPORT: February 16, 1939, Epidermoid Carcinoma.

TREATMENT:
1. Feb.16-May 1/39, H.V., 400 KV., pelvis, 6 ports, 2200 r per port.
2. May 25/39, intrauterine radium, 40 mg. tandem, 4200 mg.hrs.
intravaginal radium, 2x30 mg. 4200 mg.hrs.

END RESULT: The primary lesion was controlled by the above treatment.

Three years - primary lesion healed; no local recurrence; no extension.
Five years - primary lesion healed; no local recurrence; no extension.

FINAL CONCLUSION: Method used and result satisfactory; no complications.

February	Years	1939	1 yr. 1940	2 yrs. 1941	3 yrs. 1942	4 yrs. 1943	5 yrs. 1944	6 yrs. 1945	7 yrs. 1946	8 yrs. 1947	9 yrs. 1948	10 yrs. 1949	11 yrs. 1950	12 yrs. 1951	13 yrs. 1952	14 yrs. 1953	15 yrs 1954
PRIMARY	Cont.	0	•	•	•	•	•	•	•	0	0	0	0	0	0	0	0
	Uncont.	•	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SECONDARY	Cont.	0	•	•	•	•	•	•	•	0	0	0	0	0	0	0	0
	Uncont.	•	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
REMOTE METASTASES	Cont.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Uncont.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
A. & W.		0	•	•	•	•	•	•	•	0	0	0	0	0	0	0	0
A.W.D.		•	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D.D.		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D.E.D.		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UNTRACED		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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FIG. 6. Graphic chart used in recording results of treatment. This sheet forms first page of clinic history.

divided preferably into two equal doses one week apart. It has not been our experience that 7,500 r at Point B cannot safely be exceeded, and we have, in a few cases, exceeded 10,000 r with no apparent harm. In general, however, 7,500 to 8,500 r is a safe upper limit.

Final Total Dosage. The final totals are added and recorded in the form shown in Figure 5 and while it is recognized that from the physicists's point of view there are objections to such additions yet in practice the advantages are very great and permit a degree of dosage control not otherwise possible. In a busy department with constantly changing personnel such control is absolutely essential in order to reach and maintain a high technical standard and

avoid serious injuries.

Use of New Radioactive Materials. It is now no longer a secret that very shortly new radioactive products will be available having a concentration such that in the space now occupied by a single small radium capsule it will be possible to have a source of radiations equivalent to half a gram or even 1 gram of radium (or indeed more if this should be desirable). Thus a technique may be predicted in which the vaginal applicator here described could be loaded with the equivalent of half a gram in each end and a similar quantity in the fundus of the uterus, omitting an applicator in the cervical canal altogether as suggested by Neary,[3] thus simplifying the dose-distribution equation to that of a triangle with radiation sources at each of its points. It would appear that some such apparatus would go far towards solving the purely physical problem of delivering any desired intensity of radiation at any point within the pelvis. But we shall still be faced with the formidable and fundamental biological difficulty of tissue tolerance which will require the highest possible degree of accuracy and skill which can be brought to bear upon it if great harm is to be avoided.

Certainly if any such quantities of radioactive materials are to be used a much higher degree of accuracy in the placing of radium applicators will be required than has been commonly employed in the past. Accurate planning of dosage will be absolutely essential, while safety of all personnel in the preparation and handling of the applicators will be vital. It is believed that all of these desirable features have been provided for in the applicator described. Calculations using various quantities of radioactive material equivalent to amounts up to 500 mg. of radium and the dosages which would be delivered at each point in the pelvis by such a technique are tabulated in Table VI.

Graphic Method of Recording Results of Treatment. The summary sheet and graphic chart in use in this Institute for recording results has been found very convenient and is reproduced in Figure 6. It provides at a glance most of the essential information required while the graphic chart shows the present status of the case and also indicates whether the follow-up is functioning properly. After the three year period has passed the information contained in the graphic chart is transferred to a master file sheet in which the complete record of all cases in the group is maintained.

SUMMARY

The paper undertakes to answer three specific questions relating to the problem of cancer of the uterine cervix.

(1) The first question is a comparison of the best surgical results with the best irradiation results. The evidence favors the latter.

(2) Second, radiotherapy is still making favorable progress and the figures quoted indicate that in the past few years there has been a gain of 20 per cent in Stage I, 15 per cent in Stage II, 5–6 per cent in Stage III, with little or no change in Stage IV. Further progress is still to be expected in the future and means to this end are suggested.

(3) A new type radium applicator is described which appears to have certain advantages in the technical application of radium to the cervix.

(4) Results of treatment at the Toronto General Hospital for the years 1929–1940 are published showing five year survivals in Stage I—74.0 per cent; Stage II—50.5 per cent; Stage III—26.8 per cent; Stage IV—4.9 per cent; all stages—35.6 per cent.

(5) A useful graphic method of recording the results of treatment is presented in Figure 6.

Medical Arts Bldg.
Toronto, Canada

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DISCUSSION

DR. CHARLES L. MARTIN, Dallas, Texas. I want first to compliment Dr. Richards on his very ingenious intravaginal radium applicator and also on his excellent five year cure rate. As you know, an absolute figure of 35.6 per cent, and I assume that his figures are absolute, is very good indeed. The radium applicator illustrated in the paper forwarded to me seemed rather large but I have no doubt that he uses others of smaller size in actual practice.

Dr. Richards works in an institution where the entire care of the patient with cancer of the cervix is placed in the hands of one man. He carefully selects the types of radium therapy and roentgen therapy which are to be given and personally oversees every detail of the entire procedure. In my opinion, this may explain much of his success.

It is my impression that he gives much credit to his rather intensive preliminary course of roentgen therapy. In this connection I want to call your attention to the fact that Pitts and Waterman have reported results equally as good as those of Dr. Richards obtained with a radium technique to which no roentgen therapy was added, and the Manchester Clinic has done almost as well with a radium technique to which roentgen therapy was added only in the presence of advanced stages of the disease. Dr. Erskine is just as certain that roentgen therapy alone is the method of choice. Since good results are obtained by such a variety of techniques we have attempted in our own clinic to select the methods which produce the highest number of cures with the lowest number of irradiation sequelae. By placing more emphasis on radium therapy and less on roentgen therapy practically all sequelae have been eliminated without reducing the cure rate.

Our most vexing problem is the correct estimation of tissue dosage. This is due to the fact that we do not have a biological unit which may be used to measure the killing effect of the various types of irradiation on the cancer cell. The biological effect produced by a given number of gamma roentgens administered in a few hours is quite different from that produced by the same number of gamma roentgens used over a period of five to seven days and certainly one cannot assume that the changes produced by a given number of x-ray roentgens delivered in a period of one month will be at all similar to those produced by the same number of gamma roentgens given in a period of a few days. Therefore, the common practice of adding gamma roentgens and x-ray roentgens in estimating pelvic dosage is not scientifically correct.

Finally, may I say a word about the revival of the Wertheim operation by Dr. Meigs. He has proved that this radical operation may now be carried out in carefully selected cases by a master surgeon with no immediate mortality. However, he has not shown conclusively that the procedure will cure any appreciable number of patients with metastatic lymph nodes situated well out in the pelvis.

I have had a rather extensive experience with metastatic cervical lymph nodes and am convinced that good surgical results are obtained in this region only when a very complete block dissection is carried out in early cases. Dr. Meigs admits that his operation cannot be called a block dissection because he must protect the blood supply of the ureter which lies near the center of the operative field. I must also confess that I am dubious of the curative value of the quantities of radiation that can be safely delivered to the sides of the pelvis in such cases with present day techniques.

There are very few surgeons in this country capable of performing the operation done by Dr. Meigs and since he still advocates radiation therapy for 85 per cent of the patients coming into his own clinic, it is certainly still the method of choice in most of the hospitals and tumor clinics in which cancer of the cervix is treated.

DR. RICHARDS (closing). There are very many questions that time did not permit me to go into fully. Dr. Martin raised a number of these. The first was with regard to the figures. On one of the slides, I tried to show that the figures used were "absolute" figures. Every case was charged against our survival rate, regardless of the cause of death. Also, those which were untraced and all cases seen but not treated, were included. In that respect, the Manchester figures are "net" figures from which all those mentioned have been excluded.

As for the size of the applicators, Dr. Martin

has not seen them, I presume. They are on exhibit in the scientific exhibit. There are four sizes, so that a selection can be made to suit any individual case. He mentioned about the control of the patient. That is extremely important, and I am fortunate in that these patients are on our own ward and under our complete control. We work with the cooperation of a gynecological consultant but we are responsible for all details of the radiation treatment. It is true that the majority of the treatments are carried out by residents who are constantly changing. Partly because of these changes in personnel, a precise technique is extremely important.

Then Dr. Martin spoke about the unwisdom of adding gamma roentgens and roentgens from x-ray therapy. I quite agree with all that and in my paper I apologized to all physicists, but practically speaking it is very convenient and the best we can do until we get a better unit of measurement.

So far as his discussion of surgical methods is concerned, I haven't any quarrel with Meigs or men of his caliber but feel that it certainly would be a retrograde step if all surgeons undertook the operation described by him. Meigs admits 10 per cent of injuries to the ureter in the cases he has operated upon, although he has had no mortality. I submit that any procedure which permits 10 per cent of serious injury is not one for widespread adoption.

Regarding fractures of the neck of the femur, we have had two; both occurred prior to irradiation. We have had no cases that could be attributed directly as being due to irradiation, although if you will study the chart which is also on file in our exhibit, you will see that there is a "hot-spot" right over the neck of the femur. Nevertheless, the importance of getting extra radiation into the side wall of the pelvis is so great and so essential that we believe six portals with two lateral fields are essential.

Finally, I believe the figures, themselves, are proof as far as there can be proof that it is possible to eradicate and control lymph nodes by irradiation. Otherwise, one could not have such a high percentage of cures in Stage III cases which, by definition, must have involvement of lymph nodes in the pelvis. Otherwise, the classification has been in error.

ROENTGEN THERAPY IN UTERINE FIBROMYOMA WITHOUT OVARIAN STERILIZATION*

By GEORGE E. PFAHLER, M.D., Sc.D., LL.D.
PHILADELPHIA, PENNSYLVANIA

MY objects in the presentation of this paper are (1) to prove that the roentgen rays have a direct action on the fibromyoma; (2) to show that the rays can cause the disappearance of a fibromyoma without affecting the ovaries; (3) to show that the ovarian function and regular menstruation can be maintained during and after roentgen treatment; (4) that a deformed fetus may develop in a patient who has had no form of irradiation previously, and the patient may then bear four healthy children even after irradiation of a fibroid, because the ovaries were protected during the treatment, and (5) that healthy children may be born after patients have had treatment for uterine fibromyoma, even when the ovaries have been included, and in whom there has been temporary amenorrhea.

There will be no attempt to argue for the replacement of myomectomy when such an operation is indicated. The roentgen treatment is indicated, however, when there is a reasonably small, interstitial fibroid, and when the alternative is a hysterectomy.

Fibromyoma of the uterus is probably the most frequent gynecological lesion encountered. Ewing[2] states, "Uterine myoma is the most frequent of all tumors, its occurrence being estimated at 50 per cent of all women over 50 years of age (Klob), and at 20 per cent for those over 35 years. The incidence reaches its acme 38.8 per cent, between the ages of 30 and 40 years (Gusserow). The negress is especially susceptible." This indicates that probably one-third to one-half of women reaching the age of forty have fibromyomas of the uterus of varying sizes. The presence of fibromyoma of the uterus, as Masson[6] has pointed out, does not necessarily mean that treatment is indicated, for in many cases, the fibromyoma is small and is not producing symptoms.

Roentgen therapy has been accepted as a form of successful treatment of uterine fibromyoma for about forty years. I treated my first patient on account of uterine hemorrhage associated with uterine fibromyoma on January 24, 1906.[7] The first patient was a surgeon who requested this type of treatment, and it was carried out without any interference with the surgeon's routine work or habits of life. She has remained well during these forty years. During these past forty years, thousands of cases of uterine myoma have been treated with success.

The generally accepted opinion regarding roentgen therapy in fibromyoma uteri is that in order to bring about cessation of hemorrhage and shrinkage of the myoma, it is necessary to stop the action of the ovaries, and it has been my opinion that the chief factor in producing therapeutic results in this group of cases is due to the action upon the ovaries, and secondarily upon the myoma itself. In a paper read by invitation before the American Gynecological Society, 1915,[8] I expressed the opinion that the action of the rays is upon the tumors as well as upon the ovaries. I also made the statement that I believed we would find it possible to cause the disappearance of uterine fibromyomas without actually destroying the action of the ovaries.

In a paper read by invitation before the Obstetrical Society of Philadelphia, in 1913,[9] I reported the case of a woman of thirty-four, in whom a fibroid tumor had been completely dissipated by roentgen treatment, and after missing two menstrual periods, normal menstruation had returned

* Presented at the Forty-seventh Annual Meeting, American Roentgen Ray Society, Cincinnati, Ohio, Sept. 17–20, 1946.

and had continued during four years up to the time of the report. In that case, no pregnancy had developed but the continuation of normal menstruation led me to believe that such was a possibility. Fränkel,[4] referring to the treatment of young women had seen repeatedly amenorrhea produced for a few months, then the patient became pregnant and gave birth to a perfectly healthy child. Stern[11] in a paper published in 1915, reported 2 cases of pregnancy in young women who had been treated for uterine fibromyoma over a period of time by roentgen therapy. The *first* patient was a young woman who was thirty-two and had been married ten years, had one child eight years of age, and the patient was suffering from multiple fibroids with excessive hemorrhage. Between February and August, 1912, the patient received thirty-four fractional roentgen treatments. At this time, during the treatment, Dr. Brettauer found the patient so much improved that he advised discontinuing treatment. The patient menstruated normally up to November, when menstruation ceased. On July 26, 1913, a baby boy weighing $6\frac{3}{4}$ pounds was born. Both the pregnancy and the labor were normal. The *second* case was a young woman who had a uterine fibroid of considerable size, with irregular and profuse menstruation. She had sufficient roentgen treatment to diminish the size of the fibroid, and to produce a temporary amenorrhea. She afterward became pregnant and went through a normal labor, and was delivered of a normal child.

In a letter dated January 28, 1946, in answer to an inquiry by me, Dr. William E. Costolow of Los Angeles Tumor Institute (personal communication), writes: "It has always been my opinion that a good deal of the effects from the irradiation on fibroid is due to a direct action of the rays on the tumor itself, although I realize that this has not been so generally accepted. Certainly, in some of the large multiple fibroids which we have had to treat at times, some of the effects must have been due to the direct action on the tumor itself." This inquiry was made after reading Costolow's[1] report on the treatment of uterine fibromyomas. Costolow analyzed 986 cases, treated between 1927 and 1937. In this group they had found records of *3 patients who were irradiated and later had normal pregnancies.*

Frances A. Ford,[3] of the Mayo Clinic, Rochester, Minn., says, "Pregnancy with the birth of a normal child has been observed following radium therapy." She refers to Castaño who reported on 250 cases of fibromyomata, treated by irradiation, and 3 of the patients became pregnant following treatment. Ford says, "Of 1013 patients treated with radium at the Mayo Clinic between 1915 and 1925, Stacy found that four women each had a living child. Three others had given birth to dead fetuses; one had had two miscarriages, and one was pregnant at the time of her report. In a series of 741 myomectomies reviewed by Stacy, 33 women later had a viable child, and 11 women two or more children." Unfortunately, Stacy's report and other reports do not indicate just how many patients or what percentage of patients in either group were in the child-bearing period. We all know that the fibromyomata give rise to symptoms, usually after the usual active child-bearing period has passed. It is self-evident that only relatively young women who are in the active child-bearing period would likely become pregnant anyway, and therefore this small number of cases does not form a basis for any percentage value as to the likelihood of pregnancy following irradiation.

Ford continues, "Schiller reports the history of a woman aged 43 who had never been pregnant. Premature menopause was induced by roentgen rays because of excessive bleeding. Definite fibromyomata were present in the uterus. *Six months after treatment, menstruation reappeared once, after which the patient became pregnant and delivered a full-term baby which was normal at observation, 18 months later.*"

Ford, in her paper, refers to 3 patients who gave birth to dead fetuses. There is no record as to whether this treatment was

given to patients who had already become pregnant before or after the irradiation has ceased. It is generally believed that if damage has been done to the ovaries, ova will degenerate before they are expelled from the graafian follicles.[12]

Of the cases reviewed by Ford, 3 of the *surgical* group were under thirty, but in such condition that myomectomy proved to be impracticable. Five of the patients treated by *irradiation* were under thirty; *3 of the 5 had normal pregnancies following radium treatment*, all of these being included among the cases reported by Stacy.

Stacy reports the case of a patient, aged seventy-six, who had passed through the normal menopause at fifty-two, had first noticed the pelvic tumor four years before her treatment at the Mayo Clinic, and during these four years, the growth had been quite rapid. Ford says, "Instances of this type discredit the hypothesis that the growth of fibromyomata is stimulated by an ovarian hormone or interaction of ovarian and uterine tissues." She says, "Ewing mentions sterility as one of the possible causes of fibromyomatous tumors. Among the large number of patients having fibromyomata, Young found sterility in 31 per cent, while for all women sterility was found in about 10 per cent. It is more generally believed that the fibromyomata are a cause of sterility by mechanical irritation or obstruction, rather than a result of it."

Zimmern and Brunet[12] state, "This condition [uterine fibromyoma] affects one-fifth of all women older than 30 years." These authors point out that the effect of irradiation is almost entirely on the ovary; development of the follicle is suppressed so that the corpus luteum is no longer formed and the myomas no longer receive the stimulus of the ovarian hormones concerned with proliferation, congestion and hemorrhage. These authors do not exclude from irradiation tumors larger than a four months pregnancy. They explain, "Some evidence that irradiation affects the fibromyoma directly as well as indirectly is provided by the regression following irradiation of myomas in women already past the menopause: by continued regression of a myoma despite resumption of menstruation: by the reduction of the tumor without interruption of the menses, and by diminution in size of irradiated myomas occurring in the cervical stumps of women after removal of the uterus and ovaries."

Zimmern and Brunet give the following indications for surgical treatment: "doubtful diagnosis, coexistent infectious complications; necrotic, pedunculated, submucous, or interligamentary tumors; coexistent ovarian cyst or salpingitis; presence of a polyp in the cases in women in the child-bearing age." They irradiate all other ovarian fibromyomas. All others can be treated by irradiation and according to my records, those with intramural myomas in women who are in the child-bearing age.

The clinical record of the following cases are of first importance because of the long period of observation and the clinical history.

CASE 1 was reported first by McGlinn and myself[10] before the Obstetrical Society of Philadelphia April 5, 1917, and I quote the following history as given by Dr. McGlinn on that occasion:

> A primipara, age twenty-four, was first seen May 18, 1915, in consultation with Dr. George Mintzer. She was then five months' pregnant and complained of excruciating pain in the sacral region and aggravated nausea and vomiting. Dr. Mintzer diagnosed the case as one of pelvic tumor complicating pregnancy. On examination, I found a large soft boggy mass filling the hollow of the sacrum, the cervix displaced high in the pelvis, anterior and the uterus enlarged to correspond with five months' pregnancy. The mass posteriorly seemed to be part of the uterus and there was a sharp angulation on the posterior uterine wall between the mass and the cervix. Several days previously I had seen and operated upon a case of incarcerated retro-displaced pregnant uterus which presented the same symptoms and physical signs and which had been mistaken for a pelvic tumor. I, therefore leaned strongly toward the diagnosis of incarceration in this case. Attempts at reposition of the uterus failed. It was then advised that reposition should be tried under anesthesia and

if this failed reposition should be accomplished by abdominal section.

She was admitted to St. Agnes Hospital and on the following day, May 19, 1915, manual reposition under ether failing, the abdomen was opened. Instead of an incarcerated fundus, we found a myoma, the size of a large orange, growing from the posterior wall of the uterus completely filling the hollow of the sacrum. The tumor was soft and apparently not encapsulated and it was impossible to remove the tumor except by hysterectomy. After consulting with her husband and parents, it was decided not to interfere with pregnancy and to deliver her, if she went to term by Cesarean section if the tumor interfered with normal delivery. Fortunately, she aborted, one week after operation, an acephalic monster. She made an uninterrrupted recovery from the operation and miscarriage and left the hospital in three weeks.

She was next seen September 22, 1915. The uterus was anterior and well involuted. The tumor on the posterior wall was only slightly smaller than when last seen. A small fibroid nodule the size of a walnut was also found at the left uterine cornua. This growth was not noticed previously.

The patient was very anxious for children and refused hysterectomy. I then took up the question of x-ray treatment with Dr. George E. Pfahler. Dr. Pfahler was averse to treating the patient on account of her demands that pregnancy should not be interfered with by any treatment we should adopt. Finally after a thorough understanding with the patient, it was decided to attempt to irradiate the tumor and to protect the ovaries as far as possible. Accordingly, I mapped out the exact situation of the tumor for Dr. Pfahler who improvised a special technic for the treatments. No attempt was made to treat the small growth of the fundus of the uterus and the treatments had no effect upon it.

Patient next seen December 30, 1915. Has had three x-ray treatments. Backache better; menses regular, last four days. Mass on posterior wall much reduced in size. No longer fills the culdesac: feels size of small egg.

January 27, 1916. X-ray treatment January 26, 1916. No change in size of mass since last examination. Normal menstrual period two weeks ago.

February 16, 1916: Menstruated normally from February 9 to 14th. Tumor seems slightly smaller.

March 24, 1916: Last normal period February 9 to 14. Three weeks later had slight bloody discharge which lasted two days, had not seen anything since. The uterus is larger than at the last examination, the bulk of enlargement being due to the tumor at the left cornua. The question of possible pregnancy was considered though the patient had been warned to avoid pregnancy until we gave our consent. She admitted having had intercourse but stated that withdrawal was practised.

April 27, 1916. Normal menses on April 7. Tumor smaller.

June 28, 1916. Mass on posterior wall of uterus entirely gone. Tumor still present at left cornua. Advised to resume normal sexual life.

October 25, 1916. Last menstrual period September 8 to 12. No definite signs of pregnancy present. No change in the nodule at the left cornua of uterus. No evidence of original mass in posterior wall of uterus.

March 12, 1917. Last menstrual period September 8 to 12. Felt life about the middle of January. Uterus enlarged to correspond with the sixth month of pregnancy. Diagnosis: Pregnancy at sixth month. Pelvis entirely free. No evidence of original growth on posterior wall of uterus. Nodule at left cornua still present and slightly enlarged.

Record of Pregnancies after Irradiating the Fibromyoma. On June 30, 1917, a perfectly healthy baby girl was born but died at fifteen months of age, during the influenza epidemic of 1918. On October 12, 1918, twin boys were born (now aged twenty-eight). One weighed 5 pounds and the other 8 pounds at birth. The larger boy has always remained heavier. The smaller one at the age of twelve developed some lung condition, thought to be early tuberculosis. After about three months of care by a local practitioner, the lungs cleared and he has remained well since. Both twin boys at the age of twenty-eight are well, normal mentally, and are reported to be slightly above the average in mental development. Both boys were first-class scullers. Both boys served in the Army for two years. The larger boy is engaged to be married.

The youngest son was born in 1925, and had served in the Navy three years and seven months at the time of the last report. He is now twenty-one years of age and well. The record, therefore, indicates the birth of four healthy children after irradiation of the uterus, but with protection of the ovaries. One died at the age of fifteen months but from acute infection. The other three served in the Army and Navy.

The mother died of heart disease November 17, 1939. The father had died in 1934.

Technique. Because of the fact that uterine fibroids have been successfully treated by means of the roentgen rays after the menopause, and because of the favorable effect of deep roentgen therapy on all types of tumors, Dr. McGlinn and I reasoned that the fibroids in the uterus should be favorably influenced without directing the rays through the ovaries. Fortunately this patient was a favorable case to test this theory. The fibroid was in the median line, and occupied the posterior wall of the

uterus. Its exact position had been determined at the exploratory operation. Granting that the ovaries were in normal position the location of this tumor we reasoned would permit the direction of the rays to the fibroid without passing them through the ovaries. Acting upon this theory, treatment was given entirely through the median area, the ovarian regions being protected. On October 14, 1915, three full erythema doses were given through three different portals of entry in the median space anteriorly, and two similar full doses were given in the median region posterior so directed that they would reach the fibroid in the uterus without reaching the ovaries.

One month after the first course of treatment was given the patient reported that her last menstrual period was the first painless one that she had ever had, and the first in which she did not have to go to bed. She also reported that she could then lie on her side without discomfort. The second course of similar treatment was given on November 10, 1915, three doses anteriorly in the median line, and four doses posteriorly in the median line and through the sciatic notch. The third course of treatment was similarly given on December 8. On January 5, a fourth course of treatment was given, three doses anteriorly and two doses posteriorly. Penetrating rays were used corresponding to No. 9 on the Benoist scale, filtered through 4 mm. of glass and 2 mm. of aluminum, with 40 milliampere-minutes at a distance of 8 inches, and confining the rays strictly to the area treated.

CASE II. Mrs. H. A. T., aged thirty-seven, was referred to my office by Drs. H. M. Goddard and Collin Foulkrod, July 3, 1924, for roentgen treatment of fibromyomata. Drs. Teller and Foulkrod had advised hysterectomy which the patient had refused. Dr. Teller had reported to Dr. Goddard as follows: "She has a mass of subperitoneal fibroid tumors. They do not give her any symptoms at present, but at her comparatively young age from the size at present they will grow rapidly and will produce symptoms by their size. Remedy is a hysterectomy. Taking into consideration the value of radium and x-ray in these cases, they should only be used where a radical operation would be hazardous to the life of the patient."

Dr. Foulkrod reported that she had consulted him on November 25, 1923, after having missed two periods. She had been previously married ten years with no pregnancy though every effort had been made toward pregnancy. She had five months in her second marriage. Dr. Foulkrod found her uterus enlarged to the size of a five months pregnancy. She went to her old home in Toledo, Ohio, where she miscarried. On April 7, 1924, Dr. Foulkrod found a fibromyoma in the left cornua the size of a grapefruit, the one in the right cornua was the size of an apple. She refused operation and chose roentgen treatment.

In this case, I used high voltage roentgen treatment 210 kv., 2.5 ma., 32 cm. distance, and a 50 per cent erythema dose, filtered through 0.5 mm. copper. Two such doses were given through each side of the pelvis, one dose in the center anteriorly and two similar doses through each side posteriorly, totalling nine 50 per cent skin erythema doses (measured in air) between July 7 and October 6, 1924. She had only one menstrual period after treatment was begun on July 7, 1924. Amenorrhea occurred from August 24, 1924, until March, 1925.

On December 17, 1925, Dr. Foulkrod found the uterus had been reduced to the size of a two and a half months pregnancy and still retained some of the fibroid nodules. She was not seen again until July, 1926, when she was prepared for delivery, which was a normal primiparous labor. She was delivered by low forceps, because of a rigid perineum. After delivery Dr. Foulkrod was unable to locate any fibroids.

The patient reported to me for examination on March 13, 1928. She was perfectly well and brought a picture of her beautiful sixteen months baby girl, who is now a beautiful young lady, twenty years of age, and is a private secretary.

This case does not belong strictly under the above title, but the miscarriage before irradiation, the complete disappearance of the fibroids with only six months of amenorrhea, and then regular menstruation, and a successful pregnancy and normal delivery at the age of forty, with a normal child, justifies its inclusion.

CASE III. Mrs. M. H., a white woman, aged thirty-five, brought to me by her husband on December 27, 1938, at the request of Dr. Ralph Getelman, because a diagnosis of uterine fibroid had been made by Dr. Roy Mohler and by Dr. Franklin Payne, Professor of Gynecology at the University of Pennylsvania. She had been suffering from excessive menstruation during nineteen years, was anxious for pregnancy, and complained of backache, fatigue, and lack of

"pep." On December 27, 1938, I reported to the husband and sent a copy to Dr. Mohler, who had been her family physician during most of the time, as follows:

I find that she has a small fibroid about the size of an English walnut, located on the right side of the uterus, with the uterus retroflexed. She has had extensive menstruation during the past nineteen years. She is anxious to become pregnant, and has the idea that the fibroid is preventing the pregnancy. This is possible but I am rather doubtful that that is the cause on account of the fact that she has had this excessive menstruation during these nineteen years. If we were only treating the fibroid and not paying any attention to anything else, I would recommend x-ray treatment. However, there is more chance of her becoming pregnant by the removal of this fibroid surgically than if we treated her by irradiation. I believe however that neither you nor she should assume that she will become pregnant immediately even if this fibroid is removed surgically.

The patient and the husband decided upon having roentgen treatment. She returned to me for treatment on March 6, 1939, approximately three months after my first examination. I should add that on a previous occasion she had been taken to the hospital by Dr. Mohler for an operation and was prepared for the operation but she became fearful and would not go through with it. Accordingly treatment was begun on March 6, 1939. These treatments were given anteriorly to the uterus through a field corresponding to the size and location of the uterus and protecting the ovarian region on each side. She was given treatment anteriorly March 6, 10, 15, 1939, using 180 kv., 15 ma., 18 minutes, at a distance of 50 cm., with 0.5 mm., copper filtration, using 60 per cent erythema dose, or 450 r, at each of these treatments. Similar dosage was given posteriorly March 7, 13 and 17, 1939, making a total of 1,350 r, both anteriorly and posteriorly, and one perineal dose was given on November 15, 1939. This represents a total skin dose of 3,150 r, or a total uterine dose of 1,260 r. When examined on January 17, 1940, her menstruation was regular, and pelvic examination showed nothing abnormal. Her pruritus vulvae was gone and she seemed to be well. When examined last on December 6, 1944, she was free from symptoms, uterus normal, cervix normal, no tenderness or abnormalities about the ovarian region. Her menstruation had been regular without interruption, but she had not become pregnant. This was approximately six years after beginning the treatment of her uterine fibroid which was successful in eliminating the fibroid and restoring her to health without interrupting the menstruation.

Case IV. Mrs. E. G., aged twenty-nine, was referred to me on September 30, 1935, by Dr. Edgar J. Fiestal of Trenton, N. J. Patient had been married nine years and during this time had never been pregnant. She was anxious for pregnancy. Her periods had been very irregular. In the last two periods, she had flooded considerably. The July menstruation lasted fourteen days, in August seventeen days. Gynecological examination showed fibromata of the uterus, and roentgen treatment and radium treatment were advised in preference to surgical intervention. The gynecologist recommended roentgen treatment confined to the uterus because he felt that if he operated, he would have to remove both uterus and ovaries because both ovaries showed a cystic condition, and because of the fact that at her age she was anxious to have children.

Treatments were given with high voltage roentgen rays, using 200 kv., 4 ma., 40 cm. distance, and 0.5 Cu filtration, 225 r given eight times anteriorly, and eight times posteriorly, between September 30 and November 30, 1935. The total skin dosage was 3,600 r or approximately 1,440 r in the uterus. The ovaries were protected.

Her menstruation remained regular. She became pregnant and following the death of her father, she gave birth to a premature "blue" baby boy February 6, 1938, who lived one day. She again became pregnant almost immediately and gave birth to a normal son May 19, 1939, estimated to be one month premature. Labor had been forced because of albuminuria. The son weighed 5 pounds 6 ounces. He is now well at the age of seven. Her menstruation has remained regular ever since the treatment, except during pregnancy.

DISCUSSION

This report involves 4 cases in which roentgen therapy was used in the treatment of uterine fibroids of the interstitial type. The ovarian regions were protected by lead and in none of the four was menstruation interrupted. Two of these were followed by a total of six pregnancies. All of the children were normally formed. The first woman

had four healthy children. Three are living today. The oldest two are twenty-eight years of age. The first one died during childhood from causes not related to irradiation (infection). The other three have been in military service and have been normal in every respect.

In the second case, two children were of premature birth, which were believed by the attending physician to be due to accidental causes not related to the irradiation. One is well at the age of seven. Her menstruation is still normal, but further pregnancy has been avoided because of the cardiac disease in the husband.

The third case treated deliberately with protection of the ovaries to avoid sterilization has had no interruption of menstruation, but has not been pregnant during these seven and a half years since roentgen treatment between the ages of thirty-five and forty-three.

A fourth case received some treatment over the ovaries and had an interruption of menstruation for six months. She then became pregnant at the age of thirty-two, and again at thirty-three, and now the child is a healthy girl aged twenty.

In all these cases, the fibroid disappeared completely. The possibility of the development of carcinoma after radiation therapy for fibroid is raised as an objection sometimes. On this point, I quote from Macfarlane:[5] "From our own experience and from this review of the scanty literature of the subject, it is evidence that the possibility of carcinoma developing in the uterus after radium or x-ray treatment is very remote. This possibility does not contraindicate radium or x-ray treatment of myomatous tumors nor of climateric bleeding."

1930 Chestnut St.
Philadelphia, Pa.

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Vol. 58, No. 6

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

Editor: Lawrence Reynolds, M.D. *Assistant Editor:* Ruth Bigelow, B.S.

Editorial Board: A. C. Christie, M.D. E. H. Skinner, M.D. Lauriston S. Taylor
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Collaborating Editors: The Officers and Committee Members of the Societies of which this Journal is the official organ, whose names appear on this page, are considered collaborating editors of this Journal. *Foreign Collaborators:* Gösta Forssell, M.D., Stockholm, R. Ledoux-Lebard, M.D., Paris.
Publisher: Charles C Thomas, 301–327 East Lawrence Avenue, Springfield, Illinois.

Issued Monthly. Subscription $10.00 per year, $11.00 in Canada and $12.00 in foreign countries. Advertising rates submitted on application: Editorial office, 110 Professional Building, Detroit, Mich., Office of publication, 301–327 East Lawrence Avenue, Springfield, Ill. Information of interest to all readers will be found on page iv.

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EDITORIALS

NATIONAL SCIENCE FOUNDATION

IT HAS been more than two years since the publication of the report of the committee headed by Dr. Vannevar Bush entitled "Science, the Endless Frontier". Following that publication and after prolonged study by a sub-committee of the Senate Military Affairs Committee, proposals were made for establishment of a National Science Foundation. During the summer of 1945 Senator Kilgore introduced a bill based on the study of this sub-committee and at the same time Senator Magnuson introduced a bill modeled upon the recommendations of Dr. Bush. Both of these bills provided for establishment of a National Science Foundation within the Federal Government with the following objectives: To support financially and promote basic scientific research, research for the national defense, research for advancement of medicine and health and to establish and support scholarships and fellowships for the development of the latent scientific talent throughout the Nation. There was general agreement at the time both inside and outside Congress upon the general aims but marked disagreement on several features of both bills, especially the method of administration of the proposed Foundation. In the spring of 1946 the differences were somewhat composed and a bipartisan bill called the Kilgore-Magnuson-Saltonstall bill was passed by the Senate early in July with only one amendment, namely, that which eliminated a Division for the Social Sciences. The bill was not passed by the House. The matter was revived in the House of Representatives in the first session of the 80th Congress in the early spring of 1947. In March, the House Committee on Interstate and Foreign Commerce held hearings on four identical bills, H.R. 1815, H.R. 1830, H.R. 1834 and H.R. 2027, and on a separate bill introduced by Mr. Celler which was essentially a revival of the Kilgore-Magnuson-Saltonstall bill. At the same time the Senate had under consideration a new bill, S. 526, identical in content with the four identical House bills. The most important difference between Mr. Celler's bill and the five identical bills is the method provided for administration of the Foundation. While the Celler bill provides for a single Administrator responsible directly to the President, the five identical bills provide for a Commission of 24 to 48 members who shall elect a Director, the latter to operate under direction of an Executive Committee. One of the identical bills, S. 526, was passed by the Senate on May 20, 1947 and by the House on July 16, 1947. The bill went to the President and was vetoed by him on August 6. Numerous reasons were given for the veto but they all revolved about the methods of organization and administration of the proposed Foundation. The following quotations from the veto message will serve to indicate the President's chief objections to the bill:

. . .

. . . this bill contains provisions which represent such a marked departure from sound principles for the administration of public affairs that I cannot give it my approval. It would, in effect, vest the determination of vital national policies, the expenditure of large public funds and the administration of important governmental functions in a group of individuals who would be essentially private citizens.

. . .

. . . , the organization prescribed in the bill is so unwieldy that there is grave danger that it would impede rather than promote the Government's effort to encourage scientific research.

. . .

Under S. 526 the powers of the proposed foundation would be vested in 24 members. . . . These members would be part time officials required to meet only once a year. This group would in turn select biennially from among its 24 members an executive committee of 9 members, and would exercise its powers through the executive committee.

. . .

The foundation would have a chief executive officer, known as the director. He would be appointed by the 9 member executive committee. . . . The power and duties of the director would be prescribed by the executive committee.

. . .

There would be within the foundation a number of divisions. . . . There would be no limit upon the number of divisions which the foundation could establish.

. . .

The foundation would also be empowered to appoint commissions in various fields of research.

. . .

Apart from the conflicts and confusions which would result from this complex organization, the bill would violate basic principles which make for responsible government.

. . .

Full governmental authority and responsibility would be placed in 24 part-time officers whom the President could not effectively hold responsible. . . . Neither could the Director be held responsible by the President for he would be the appointee of the Foundation and would be insulated from the President by two layers of part-time boards. In the case of the divisions and the special commissions, the lack of accountability would be even more aggravated. . . I am convinced that the long-range interests of scientific research and education will be best served by continuing our efforts to obtain a Science Foundation free from the vital defects of this bill.

I hope that the Congress will reconsider this question and enact such a law early in its next session.

It seems clear from the language of the veto message that a bill acceptable to the President is one which provides for a single administrator responsible directly to the President, such as the bill sponsored by Mr. Celler at the last session of Congress. Examination of the latter bill, however, shows that its organization into divisions and committees is fully as extensive and complex as in the vetoed bill. Whether it would meet the President's objections if passed is not known.

Study of the testimony presented before the Committee on Interstate and Foreign Commerce of the House of Representatives discloses a general consensus that the most important objectives of a National Science Foundation are basic science research and the training of a large number of new scientists through scholarships and fellowships supported by federal funds. It is obvious, but should be emphasized, that research in basic science depends upon the existence of trained scientists. It follows that among the purposes stated in the various proposed bills, that which provides for establishment of scholarships and fellowships is fundamental. No effective or continuing scientific research can be carried on unless our educational system is organized for continuous training of the individuals who have the qualifications for such training. There was much testimony before the Congressional Committee to show that federal subsidy is necessary to enable a large number of well-qualified High School students to go to college and to further pursue the study of science in post-graduate years. The following quotation from the testimony of Dr. Conant emphasizes this point: "Granted that in terms of the industrial development of the Nation, in terms of public health, and above all in terms of military strength we must find and train our scientific talent, you may ask why a federally supported program of scholarships is required. I wish that all who raise this question could take the time to read the last section of the document entitled 'Science, the Endless Frontier.' The answer to the doubting Thomases is there set forth in detail. . . . The facts presented in that report and in other documents prove convincingly that we have been to a large degree wasting our most valuable national

asset: the innate ability of each new generation."

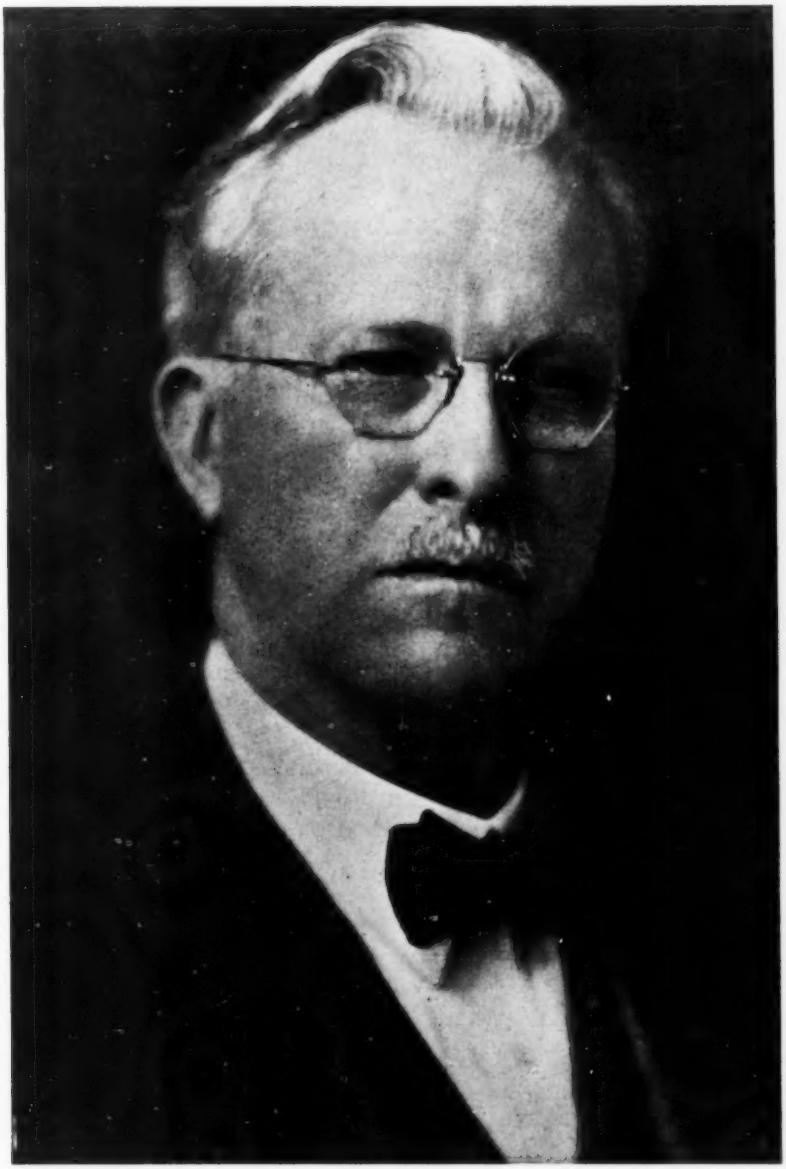
With only a few exceptions those who testified before the congressional committees strongly supported the view that to accomplish the proposed objectives it is essential to establish a Science Foundation within the Federal Government. In view of the failure to pass legislation to accomplish this, it seems pertinent to inquire whether these objectives can be attained by other means than the establishment of new and elaborate governmental machinery. Is it not possible to so strengthen the many already existing research agencies within the government that basic scientific research will be advanced quite as effectively as through the operation of a Foundation? There are many precedents for appointment of an advisory board of scientists which could make a survey of the work being done in existing agencies and of their personnel and facilities and which could continuously advise concerning the necessity for new projects and the places where they could be worked out to the best advantage. It is admitted by all that most of the basic scientific research work, whether it is initiated by a National Science Foundation or by others, will be carried out in existing university laboratories. Basic research could conceivably be greatly increased by judicious appropriations made by Congress upon the recommendations of such an advisory board as that mentioned above and administered by existing government research departments or by the National Research Council. The latter organization has the machinery and experience to do this very thing. It would also seem feasible for the same agency to administer federal funds in almost any amount for scholarships and fellowships in preparation for scientific careers since it has been doing similar work through grants from private foundations for a long time.

In the field of medicine and health, with which we are concerned, there is special need for basic research. Medicine is often reproached for its slowness in providing a cure for cancer. The critics point to the rapidity with which the atom bomb was produced when money was furnished in unlimited amounts and scientists organized to do the job. Such critics ignore the fact that the basic research upon which the wartime work depended had been done before the war began. The problem of producing the atom bomb was largely a technological one. The same may be said of radar and of other advances made during the war. The conditions are quite otherwise in providing a cure for cancer. The essential basic facts concerning this disease are not yet known. There is no way of knowing how much basic research must yet be done before we have sufficient knowledge to develop the technique for its cure. It will probably come a little at a time in laboratories scattered over the world. The government has already established its agency for research in cancer within an already existing governmental department, the United States Public Health Service. If there are projects which can be carried out in this field which cannot be done at the National Cancer Institute but require research at some other laboratory, it would seem practicable for the Congress to furnish the funds for such research and to permit the necessary administrative work to be done by the ad-administrative officers of the National Cancer Institute.

The necessity for accelerating basic scientific research is so vital for national defense, for the health of the people and for the progress of industry, and the need for the training of scientists is so urgent, that other methods should be sought at once instead of waiting for the slow processes of legislation to perfect a law which is acceptable to all.

ARTHUR C. CHRISTIE, M.D.

1835 Eye St., N.W.
Washington 6, D. C.



JAMES MADISON MARTIN
1867–1947

DR. JAMES MADISON MARTIN died on September 26, 1947, at the age of eighty in Dallas, Texas, after a long illness.

He was born on a farm in Phelps County, Missouri, on December 11, 1867. He disliked farm work and while still a young man associated himself with a master mechanic who taught him shop work and cabinet making. He maintained an interest in mechanics during his entire life and even in his later years spent much of his spare time in making beautiful pieces of furniture.

Dr. Martin's early education was obtained at the Valparaiso Normal and Business Institute in Indiana and the Vichy Normal and Business Institute in Vichy Springs, Missouri. Although he had no formal instruction in mechanical drawing he taught himself how to draw and became so expert with a pen that he was asked to teach penmanship which was considered an important accomplishment in the early nineties.

His medical degree was obtained at the St. Louis College of Physicians and Surgeons in 1890. In 1892 he became a general practitioner and settled in the small village of Massey, located in the black land belt of Texas. At this location he built a rather elaborate drug store equipped with a laboratory for bacteriological and blood studies, an ambitious undertaking for a physician located in the ranch country twelve miles from a railroad. In 1893 he was married to Emma Auerbach of Edgar Springs, Missouri.

Since country practice was strenuous and not too remunerative he moved to Hillsboro, Texas, in 1901 where he equipped an office. His interest in mechanics induced him to obtain a wall plate and a static machine about which he knew so little that he took an extensive correspondence course in electrophysics. In 1903 one of Pusey's first articles on the treatment of skin cancer with roentgen rays fell into his hands and he elaborated a similar technique which is still considered a very useful procedure.

After attending the annual meeting of the American Roentgen Ray Society in St. Louis in 1904 he became a member. His file on the AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY starts with the printed transactions of the Society for the meeting held in 1902 and during most of his professional life he took an active interest in the national radiological societies.

In 1904 he accepted the professorship in "Electro-Therapeutics and X-ray Methods" in the Dallas Medical College. It was necessary for him to travel sixty miles to Dallas to give each lecture and in 1906 he moved to Dallas where he set up one of the first laboratories in the Southwest devoted exclusively to the use of electrical methods and roentgen rays in medicine. In those early days no suitable textbooks were available and Dr. Martin prepared a mimeographed syllabus for his lecture course, illustrated with blue prints which he made himself. This material was published in book form by the C. V. Mosby Company in 1912 under the title "Practical Electrotherapeutics and X-ray Therapy." The section on skin cancer illustrates results which cannot be excelled today.

Dr. Martin served as Professor of Radiology in the Baylor Medical School for many years and was Professor Emeritus of Radiology in the new Southwestern Medical College at the time of his death. He was a past president of the Texas Radiological Society; the Dallas County Medical Society; the Dallas Southern Clinical Society; the Dallas Doctors' Luncheon Club; the Texas Geographic Society, and the American College of Radiology. He was 32d degree Scottish Rite Mason and a Shriner and a charter member of the Dallas Athletic Club. He was also a Rotarian and a member of the Dallas Bonehead Club. During his entire lifetime he was deeply interested in photography and he made many excellent motion pictures, many of which were in color.

Dr. Martin was a true pioneer in the practice of radiology to which he lent a constant enthusiasm and a degree of energetic support which will not soon be forgotten in the Southwest.

He is survived by one son, Dr. Charles L. Martin, with whom he organized the Martin X-ray and Radium Clinic in Dallas in 1940, and a grandson, Dr. James A. Martin who is now a Lieutenant (JG) in the Navy.

FORREST C. SWEARINGEN

1885–1946

DR. FORREST C. SWEARINGEN, a member of the American Roentgen Ray Society since 1921, died on March 24, 1946, at his home in Pomona, California. After being in failing health for several years, he died from hypertension and uremia.

Dr. Swearingen was born on December 16, 1885, in Sac City, Iowa, and was a member of the class of 1914 at Rush Medi-

cal College. He resided in California from 1915 until his death. He served in the Medical Corps of the United States Army in World War I from August 7, 1918, until February 1, 1919, and was the second commander of the Charles P. Rowe Post of the American Legion. He practiced radiology in Pomona in association with Drs. E. E. Kelly, George D. Brown, and John Staub.

Among the societies and organizations of which Dr. Swearingen was a member are the Los Angeles County Medical Society, the California Medical Association, the American Medical Association, the Radiological Society of North America, the Pacific Roentgen Society, and the American Cancer Foundation, of which last he was a patron member. He was also a Mason and an Elk, and was past president of the Pomona Rotary Club.

His mother, Mrs. Flora B. Swearingen, his wife, Winifred Morrison Swearingen, and one son, Richard Lee Swearingen, survive him.

RAMSAY SPILLMAN

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual meeting: Palmer House, Chicago, Ill., Sept. 14–17, 1948.

American Radium Society
Secretary, Dr. H. F. Hare, 605 Commonwealth Ave., Boston, Mass. Annual meeting: Chicago, Ill., 1948.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: Hotel Statler, Boston, Mass., Nov. 30–Dec. 5, 1947.

American College of Radiology
Secretary, Mac F. Cahal, 20 N. Wacker Drive, Chicago 6. Annual meeting: Continental Hotel, Chicago, Ill., June 20, 1948.

Section on Radiology, American Medical Association
Secretary, Dr. U. V. Portmann, Cleveland Clinic, Cleveland, Ohio. Annual meeting: Chicago, Ill., June 21–25, 1948.

Alabama Radiological Society
Secretary, Dr. C. S. Stickley, 515 Bell Bldg., Montgomery, Ala. Next meeting time and place of Alabama State Medical Association.

Arkansas Radiological Society
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Brooklyn Roentgen Ray Society
Secretary, Dr. A. H. Levy, 1354 Carroll St., Brooklyn 13, N. Y. Meets monthly on fourth Tuesday, October to April.

Buffalo Radiological Society
Secretary, Dr. Joseph S. Gian-Francheschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse, N. Y. Three meetings a year. January, May, November.

Chicago Roentgen Society
Secretary, Dr. T. J. Wachowski, 310 Ellis Ave., Wheaton, Ill. Meets second Thursday of each month October to April inclusive at the Palmer House.

Cincinnati Radiological Society
Secretary, Dr. Eugene L. Saenger, 735 Doctors Bldg., Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. George L. Sackett, 10515 Carnegie Ave. Cleveland 6, Ohio. Meetings at 6:30 P.M. on fourth Monday of each month from October to April.

Dallas-Fort Worth Roentgen Study Club
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

Denver Radiological Club
Secretary, Dr. Mark S. Donovan, 306 Majestic Bldg., Denver 2, Colo. Meets third Friday of each month at Department of Radiology, Colorado School of Medicine.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

Florida Radiological Society
Secretary, Dr. J. A. Beals, St. Luke's Hospital, Jacksonville, Fla. Meets twice yearly, in April preceding annual meeting of Florida Medical Society, and in November.

Georgia Radiological Society
Secretary, Dr. Robert Drane, DeRenne Apartments, Savannah, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. J. A. Campbell, Indiana University Hospitals, Indianapolis 7. Meets second Sunday in May.

Iowa X-Ray Club
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. Special meetings by announcement.

Kentucky Radiological Society
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

Long Island Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

Louisville Radiological Society
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Louisville General Hospital.

Michigan Association of Roentgenologists
Secretary, Dr. E. M. Shebesta, 1429 David Whitney Bldg., Detroit. Three meetings a year, Fall, Winter, Spring.

Milwaukee Roentgen Ray Society
Secretary, Dr. C. A. H. Fortier, 231 W. Wisconsin Ave., Milwaukee, Wis. Meets monthly on second Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. Chauncey N. Borman, 802 Medical Arts Bldg., Minneapolis 2, Minn. Two meetings yearly, one at time of Minnesota State Medical Association the other in the fall.

* Secretaries of societies not here listed are requested to send the necessary information to the Editor.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. Ralph C. Moore, Nebraska Methodist Hospital, Omaha 3, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. George Levene, Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. Ramsay Spillman, 115 East 61st St., New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. J. E. Hemphill, 323 Professional Bldg., Charlotte 2, N. C. Meets in May and October.

NORTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings held by announcement.

OHIO STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Carroll C. Dundon, 11311 Shaker Blvd., Cleveland. Meets during meeting of Ohio State Medical Association in Cincinnati, May, 1948.

OKLAHOMA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. P. E. Russo, 230 Osler Bldg., Oklahoma City, Okla. Three regular meetings annually.

OREGON RADIOLOGICAL SOCIETY
Secretary, Dr. William Y. Burton, 242 Medical Arts Bldg., Portland 5, Oregon. Meets monthly 2nd Wednesday, 8:00 P.M., Library of University of Oregon Medical School.

ORLEANS PARISH RADIOLOGICAL SOCIETY
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

PACIFIC ROENTGEN SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport. Annual meeting, May 21–22, 1948, Erie, Pa., at Hotel Lawrence.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. C. L. Stewart, Jefferson Hospital. Meets, first Thursday of each month, October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. R. P. Meader, 4002 Jenkins Arcade Pittsburgh 22, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, September to May.

RADIOLOGICAL SECTION, CONNECTICUT MEDICAL SOCIETY
Secretary, Dr. Robert M. Lowman, Grace-New Haven Community Hospital, New Haven 11, Conn. Meets bimonthly on second Thursday, at place selected by Secretary.

RADIOLOGICAL SECTION, LOS ANGELES CO. MED. ASSN.
Secretary, Dr. Moris Horwitz, 2009 Wilshire Blvd., Los Angeles 5, Calif. Meets on second Wednesday of each month at the County Society Building.

RADIOLOGICAL SECTION, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Roy G. Giles, Temple, Texas.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. Raphael Pomeranz, 31 Lincoln Park, Newark, N. J. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. Murray P. George, Strong Memorial Hospital. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr. Meets in Salt Lake City, Utah, 1948.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. Edwin C. Ernst, Beaumont Medical Building, St. Louis, Mo. Meets fourth Wednesday of each month, except June, July, August, and September.

SAN DIEGO ROENTGEN SOCIETY
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Wednesday at dinner.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOUTH CAROLINA X-RAY SOCIETY
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

UTAH RADIOLOGICAL CONFERENCE
Secretary, Dr. Henry H. Lerner, School of Medicine, University of Utah, Salt Lake City 1. Meets 1st and 3rd Thursdays monthly from 7:30 to 10 P.M., Salt Lake County General Hospital, September to June.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary, Dr. M. Lowry Allen, Judge Bldg., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. E. L. Flanagan, 116 E. Franklin St. Richmond, Va. Meets annually in October.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Homer V. Hartzell, 310 Stimson Bldg., Seattle 1, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

X-Ray Study Club of San Francisco
Secretary, Dr. Ivan J. Miller, 2000 Van Ness Ave. Meets monthly on third Thursday at 7:45 P.M., first six months of year at Lane Hall, Stanford University Hospital, and second six months at Toland Hall, University of California Hospital.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Mexico

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

British Empire

British Institute of Radiology Incorporated with the Roentgen Society
Medical Members' meeting held monthly on third Friday at 2:30 P.M. and Ordinary Meeting at same time on following Saturday, October to May, 32 Welbeck St., London, W.1.

Faculty of Radiologists
Secretary, Dr. M. H. Jupe, 23 Welbeck St., London, W.1 England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary, Dr. E. M. Crawford, 2100 Marlowe Ave., Montreal 28, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Francaise d'Electrologie et de Radiologie Médicales
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital. K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to November inclusive.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

South America

Sociedad Argentina de Radiologia
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Andrelino Amaral, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Tuesday at 9 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306 Lima, Peru. Meetings held monthly except during January, February and March, at the Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Alliés, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, MUDr. Roman Blána, Praha XII, Korunní 160, Czechoslovakia.

Polish Society of Radiology
First post-war inaugural meeting will be held in Warsaw, May 22 and 23, 1947.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, Nowogrodzka 59, Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad. USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 P.M.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. Babaiantz, Geneva.
Secretary for German language, Dr. Max Hopf, Effingerstrasse 49, Bern. Meets annually in different cities.

Isotopes Division Circular E-11

AVAILABILITY OF RADIOISOTOPES WITH INCREASED SPECIFIC ACTIVITIES

The Isotopes Division is pleased to announce that Clinton National Laboratory has produced a limited quantity of a number of radioisotopes which have specific activities higher than is available in usual irradiated units listed in our catalog.

The higher specific activity radioisotopes will be distributed in units containing the same quantity of radioactivity as normally present in the standard irradiated units of these isotopes listed in Radioisotopes Catalog and Price List No. 2 of the Isotopes Division. The units of the higher specific activity material will be sold at the same price as the standard unit. For example, Co 60 is routinely available in the irradiated unit. Item 19 which contains approximately 20 millicuries, cost $33 per unit and has a specific activity of 30 millicuries per gram of cobalt present in the irradiated target (Co_3CO_4). The higher specific activity cobalt will be distributed in units which contain 20 millicuries and cost $33 per unit but will have a specific activity of 250 millicuries per gram of cobalt. Such a unit should be designated as "Item 19, high specific activity," in all requests, correspondence and orders.

The above table presents the essential information on the now available materials.

Higher Specific Activity Materials now Available in Limited Quantities

Isotope	Half-life	All Units.....$33 Mc/unit	Specific activity Mc/g element		Designation
Cobalt 60	5.3 y	30	250	Item 19,	High specific activity
Iron 59	44 d	1.0	0.25	Item 39,	"
Iron 55	4 y	*	0.50		
Mercury 203, 205	51.5 d	135	60	Item 47 B,	"
Mercury 197	64 h 25	‡			
Nickel 59	15 y	1	0.8	Item 51	"
Silver 110	225 d	35	50	Item 72A	"
Tantalum 182	117 d	40	830	Item 76	"
Tin 113	100 d	1.0	0.75	Item 3 C	"
Antimony 125	2.7 y	*	¼ Mc/gm of Sn†		
Titanium 51	72 d	1	3	Item 84	"
Zinc 65	250 d	15	25	Item 91	"
Zinc 69	13.8 h				

* The quantity of activity of these radioisotopes present depend upon the age of material.

† Specific activity at the time the irradiated target is removed from the pile.

‡ These activities are present at the time the targets are moved from the pile. Due to their short half-life, little or no activities will be present when units are received.

For a listing of the isotopes concerned, see the table included in the latter part of this announcement. These radioisotopes are all produced by neutron, gamma reaction on suitable pile targets using extended irradiation periods. These irradiated targets have been dissolved in order to facilitate their measurement and distribution in the ordinarily listed quantities of activity listed in Radioisotopes Catalog.[1] Detailed analyses on the solution containing the radioisotopes are not presently available but pertinent information relative to them will be given on the memoranda accompanying shipments.

[1] Radioisotopes. Catalog and Price List No. 2. Effective March 1, 1947; Revised September, 1947. Distributed by: Isotopes Branch, United States Atomic Energy Commission, P.O. Box E, Oak Ridge, Tennessee.

Please use Form 313 when requesting allocations of these items.

In addition to the radioiron listed in the above table, another batch of radioiron having a specific activity approximately 1.8 mc. of Fe 59 and 1.5 mc. of Fe 55 per gram of the total iron (at the time the material is removed from the pile) is available from time to time. The latter material will also be distributed in units of 1.0 millicuries of Fe 59 dissolved in a suitable acid and will be sold at $33 per unit. Since there are two types of higher activity iron, one should designate the activity desired.

All radioiron produced by pile bombardment of natural iron contains both Fe 59 (half-life 44 d) and Fe 55 (half-life 4 y). Due to the difference in the half-lifes of the two isotopes, the relative quantities of the two isotopes of iron will materially change with the passage of time from that given in the table and the above paragraph. The Fe 55 content will become relatively higher as its half-life is much longer. If the radioiron is to be used in human beings, the Fe 55 content of the higher activity materials must be determined experimentally and should not be based on calculations using the quantity of Fe 59 activity received. In order to standardize sale prices, the iron units are sold on the Fe 59 content only.

October 24, 1947.

Isotopes Division Circular E-12

SEPARATED P 32, ITEM S-3, CATALOG

On and after November 19, the solutions containing chemically separated P 32 shipped from Clinton National Laboratory will be in the range of pH 3–5 instead of pH 7–9 as stated in Item S-3 of the Radioisotopes, Catalog and Price List No. 2, revised September, 1947.

This modification is being made to reduce the possibility of adsorption of P 32 on the walls of glass shipping container. Abnormal losses of activity have been noted by some recipients of P 32 shipments and experimental evidence obtained at Clinton Laboratory indicates that the losses were probably due to the adsorption phenomenon which can be minimized if the solutions containing the P 32 are in an acid state.

The other specifications of Item 3 as listed in the Catalog remain unchanged.

The supply of P 32, Item 3, has been adequate to meet all legitimate demands and can be increased if need for material warrants it.

November 10, 1947

United States Atomic Energy Commission
Isotopes Division, Oak Ridge Operations
Oak Ridge, Tennessee

GENERAL INFORMATION CONCERNING UNITED STATES PUBLIC HEALTH SERVICE RESEARCH FELLOWSHIPS

The Surgeon General of the United States Public Health Service has been given the authority to establish and maintain research fellowships. These fellowships are intended to promote the training and development of investigators in the field of medicine and related sciences.

Types of Fellowships Awarded—Stipends

1. A predoctorate research fellowship* at the Bachelor level is available to qualified applicants who have a Bachelor's Degree. This fellowship carries a stipend of $1,200 for successful applicants without dependents and $1,600 per annum for this fellowship awarded to persons with dependents. In addition, the tuition fee is paid by the U. S. Public Health Service.

2. A predoctorate research fellowship* at the Master level is available to qualified applicants holding a Master's Degree or its equivalent in graduate training. This fellowship carries a stipend, in addition to tuition fees, of $1,600 for persons without dependents and $2,000 for persons with dependents.

3. A postdoctorate research fellowship is awarded to qualified persons holding a Doctor's Degree in medical or related fields. This fellowship does not provide tuition fees but carries a stipend of $3,000 per year for Doctors without dependents and $3,600 per year for those with

* These predoctorate fellowships are also granted to medical students who, having completed one or two years of their medical course and contemplating a career in medical research, wish to spend one, two or three additional years in a basic science (biochemistry, physiology, physics, etc.) before completing their studies toward the M.D. degree.

dependents. An increase of $300 each year is granted to those Doctorate Fellows who are reappointed.

4. Special research fellowships are awarded to applicants who qualify for a postdoctorate fellowship and in addition have demonstrated outstanding ability or who possess specialized training for a specific problem. This fellowship does not carry a set stipend but is determined in the individual case.

Term of Fellowships

Fellowships are awarded for one-year periods and may be renewed. Except in unusual circumstances, Postdoctorate Fellows are not reappointed for a third year.

Time of Award of Fellowships

Fellowship applications are acted upon and fellowship awards are made at approximately three-month intervals.

Vacations

U. S. Public Health Service Research Fellows may take vacations in accordance with the rules of the institution with which they are working, but not to exceed one month during the tenure of the fellowship; vacations "earned" but not taken during the fellowship cannot be compensated for subsequent to the term of the fellowship appointment.

Travel Allowances

Travel grants are not made to Fellows except that travel expenses (first-class transportation only) may be granted from the institution of residence or from the home of the Fellow to the institution selected for fellowship training. No allowances will be made for return travel, travel of dependents, or for shipping charges for personal effects and/or household goods.

Concurrent Fellowships

U. S. Public Health Service fellowships will not be awarded or continued concurrently with the awards of other fellowships except in most unusual circumstances.

Progress Reports

Progress reports are required at the end of eight months from those Fellows who contemplate applying for reappointment and at the end of the fellowship year from all others. The person under whom the Fellow is working will be requested to submit a report on the Fellow.

Income Tax Exemption

U. S. Public Health Service has been notified by the Collector of Internal Revenue that "generally where fellowships or scholarships are awarded to individuals in order to enable them to pursue a particular line of research or study, for their improvement and benefit, and no consideration of any kind is given by the recipient in return for such an award, the amount received is considered a gift or gratuity and would not be subject to withholding tax."

Teaching by Fellows

Fellows are permitted to carry on not more than one hour of teaching or lecture or three hours of laboratory instruction per week during one semester only.

Effective Date for Beginning Fellowships

Although fellowships are awarded approximately every three months, the effective date for beginning fellowship work can be set at any time to suit the convenience of the successful applicant and the institution in which he will be working.

Application Forms

Forms of application for a research fellowship may be obtained from the Division of Research Grants and Fellowships, National Institute of Health, Bethesda 14, Maryland.

1. This application form, one copy only, is to be filled out and sent to the Division of Research Grants and Fellowships.

2. The application is to be supported by transcripts of scholastic records and when available by a statement as to relative standing in the class.

3. The application must be supported by letters of recommendation from persons named by the applicant in the application form.

4. The application must be supported by a statement from the department head or other responsible person under whom the fellowship work is to be conducted indicating that satisfactory arrangements have been made with him and with the institution. It is the responsibility of the applicant to make necessary arrangements for the conduct of the proposed research fellowship work and the work may be conducted at any acceptable institution, including governmental research laboratories, such as are provided at the National Institute of Health, National Cancer Institute, etc.

Support of the U.S. Public Health Service Research Fellowship Program

The support of this program is derived from funds appropriated by the Congress for this purpose to Institutes or Divisions of the U. S. Public Health Service; therefore, fellowships awarded will carry a designation depending upon the funds used to support the fellowship, e.g., National Cancer Institute Special Research Fellow, Division of Mental Hygiene Postdoctorate Research Fellow, National Institute of Health Predoctorate Fellow—Bachelor level, etc.

Publications

It is requested that all publications resulting from work carried on by U. S. Public Health Service Research Fellows carry in a footnote acknowledgment of the fellowship award, and that two reprints of each such report be furnished the Division of Research Grants and Fellowships.

Regardless of the field of endeavor in which the Fellow hopes to conduct his research investigation, all applications should be addressed to the Division of Research Grants and Fellowships, National Institute of Health, Bethesda 14, Maryland, where all applications will first be reviewed by a Central Qualifications Board and subsequently by one of the Specialty Fellowship Boards of the Division or Institute concerned. Similarly, all questions in regard to the Fellowship Program, both by applicants and by Fellows, are to be directed to the Division of Research Grants and Fellowships, which will be pleased to assist in any way possible.

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ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN DIAGNOSIS

NERVOUS SYSTEM

Friedl, E. Erweiterung des Wirbelkanales bei Geschwülsten des Rückenmarkes, der Nervenwurzeln and der Rückenmarkshäute. (Dilatation of the spinal canal in tumors of the spinal marrow, the nerve roots and the spinal meninges.) *Radiol. clin.*, Sept., 1946, *15*, 275–280.

Dilatations of the spinal canal are not visible in the roentgenogram unless they are very marked and caused by large tumors. These tumors may be gliomata and gliomatous syringomyelia of the cervical column, neurinomata of the nerve roots and cauda or lipomata of the spinal meninges at the lower part of the cord. Neurinomata have a tendency to grow out through the intervertebral foramen. The part of the tumor lying outside the spinal column may grow to the size of a child's head while that inside the canal may not be larger than a hazelnut. These are called hour-glass tumors. They may cause indentation of the posterior surface of the body of the vertebra, destruction of the arches as a result of dilatation of the intervertebral foramen and erosion of the inner surfaces of the arches.

Details of the changes caused by tumors of the different segments of the spinal column are described and illustrated with roentgenograms. —*Audrey G. Morgan.*

Shenkin, Henry A., Horn, Robert C., Jr., and Grant, Francis C. Lesions of the spinal epidural space producing cord compression. *Arch. Surg.*, Oct., 1945, *51*, 125–146.

This is a presentation of the spinal extradural compressive lesions encountered in a ten year period and taken from the material of the laboratory of neruosurgical pathology at the Hospital of the University of Pennsylvania. This series consisted of 54 cases and comprised, roughly, 30 per cent of the total number of mass lesions of the spinal canal. All patients studied had undergone a laminectomy for symptoms of cord pressure. The pathological material had been reviewed and correlated with the clinical course.

In the older age group, in this series, metastatic carcinoma and multiple myeloma were the most common lesions found. Usually these lesions could be detected roentgenographic methods. In the younger age groups the authors found neuroblastoma and giant cell tumors of the bone was the cause for cord compression. They also found that in the younger age group, the inflammatory processes, such as tuberculous granuloma and epidural abscess, were common. Extradural cysts were also associated with young people. In many of these conditions the clinical course and the roentgenographic findings were particular aids in evaluation of the case.—*George W. Chamberlin.*

Josey, Allen I., and Murphey, Francis. Ruptured intervertebral disk simulating angina pectoris. *J.A.M.A.*, June 15, 1946, *131*, 581–587.

When rupture of a lower cervical intervertebral disk occurs with pressure on the spinal cord or nerve roots, there is usually pain in the neck with radiation to the shoulder, precordium, or down the arm, and it may be associated with weakness or numbness. The pain may be aggravated by coughing or sneezing, or by activity which involves moving the neck. It may occur with merely change in position of the head.

In many cases the presenting symptom is pain in the chest or pain down the arm or both. Sometimes the pain is so severe that other neurological changes are not detected. Since this precordial pain, radiating down the arm, is sometimes associated with activity, coronary occlusion or angina pectoris is thought of.

Within a period of three years the authors saw 30 cases of this type, and they report 7 of these. Detailed histories are given. In one case the pain was brought on by walking a definite distance, and this finding made the surgeon hesitant to operate, despite normal electrocardiographic findings. Relief was obtained by surgical removal of the herniated disk. In another case, precordial pain occurred after successful removal of a herniated disk, and relief of this pain was obtained by neck traction. This finding, combined with other clinical and

laboratory data, established the fact that precordial pain in this patient was associated with recurrence of disk protrusion.

In many cases pressure over the brachial plexus or over the involved nerve root reproduced the pain. Pyelography was done in most cases, and electrocardiograms were obtained on most of the patients. In many, response to glyceryl trinitrate was determined.

The authors emphasize the fact that in any patient believed to have angina pectoris or coronary occlusion who presents any atypical findings, or in whom the suspected diagnosis cannot be substantiated, this syndrome is to be considered. They point out that in the case of a ruptured cervical disk, an operation may not only cure the patient but prevent the possibility of his becoming a hopeless cardiac invalid without necessarily having any heart disease at all.—*E. F. Lang.*

SELANDER, ERIC. Embryonal tumor of the sympathetic nervous system; report of two cases. *Acta radiol.*, 1943, *24*, 1–12.

The embryonal tumors of the sympathetic nervous system are relatively rare malignant tumors which arise from the common mother cells (sympathogonia) of the sympathetic ganglial cells and chromaffin cells or from cells which have become more or less differentiated in one or the other direction. They may be found in any part of the body in which the sympathetic nervous system is represented by cells but they probably arise most frequently from the ganglionated cord or the adrenal medulla. They are most common in children and are sometimes congenital. They metastasize to the liver, the lymph nodes and the bones. These tumors should be kept in mind in the presence of multiple bone changes in children. Clinical diagnosis is generally difficult due to distant metastases appearing before the primary tumor has become demonstrable.

Histopathologically, the tumor resembles small cell sarcoma. Despite considerable radiosensitivity in the primary tumors as well as the metastases, no permanent therapeutic effect has yet been secured due partly to the fact that far-reaching extension has generally already occurred when the patient comes under treatment. Then, too, there is a pronounced tendency toward recurrence.

Roentgen Picture. Two types of extension from the tumors arising in the adrenal medulla are generally cited: (1) in Pepper's type (described in 1901) the metastases are found mainly in the regional lymph nodes and the liver with clinical abdominal tumors as the result; (2) in Hutchinson's cases (described in 1907) the metastases first appear in the skeleton particularly in the orbital walls of the skull which results in exophthalmos and discoloration of the eyelids (often long before the primary tumor can be demonstrated).

In the bones the metastases grow partly in the medulla and partly subperiosteally. From the medulla the process extends to and wears away the cortex which is shown in the roentgenogram as multiple patchy areas of rarefaction which usually are well delimited. The subperiosteal metastases elevate the periosteum which generally reacts with the formation of bone. In advanced cases the line of periosteal ossification is penetrated and spicules appear at right angles to the bony surface. The changes are most commonly found in the shafts of the long bones and the skull. The metastases often develop symmetrically, particularly in the metaphyseal regions of the long bones.—*Mary Frances Vastine.*

SKELETAL SYSTEM

EINHORN, NATHAN H., MOORE, JOHN R., and ROWNTREE, LEONARD A. Osteochondrodystrophia deformans (Morquio's disease). *Am. J. Dis. Child.*, Nov., 1946, *72*, 536–544.

In 1941, the authors reported 3 cases of osteochondrodystrophia deformans (eccentro-osteochondrodysplasia). In 2 of these the disease was far advanced, and in 1 it was thought to represent an early stage. No detailed report of an autopsy on a patient with osteochohdrodystrophia deformans exists in the literature, Recently 1 of these 3 patients died and the authors now report the observations at autopsy in detail.

The patient was a ten year old boy. The roentgenograms showed, on admission to the hospital, a definite disturbance of growth in the epiphyseal centers. The long bones were shorter than normal. There was actual change in shape of some of the other bones, particularly in the bodies of the vertebrae. At the dorsolumbar junction a number of the vertebral bodies were wedge shaped, with resulting kyphosis. In the cervical region there was demineralization and loss of stature, so that the first cervical was located at the level of the foramen magnum

and farther cephalad than normal. These changes resembled those seen in basilar impression of the skill (platybasia).

At autopsy a definite abnormal relationship between the first cervical segment and the base of the skull was demonstrated. This abnormality resulted in pressure on the brain stem and upper part of the cervical portion of the spinal cord, with compression of the latter. The neuromuscular changes observed in the patient were considered secondary to compression of the cord.—*R. S. Bromer.*

Hughes, B., and Gislason, G. J. Osteonephropathy; report of two cases. *J. Urol.*, April, 1946, *55*, 330–341.

The term ostenonephropathy has been suggested for the entity in which bone changes exist in the presence of associated renal disease. This entity has been variously designated previously as renal rickets, renal dwarfism, renal infantilism, renal osteodystrophy, renal hyperparathyroidism and juvenile osteitis fibrosa. The clinical picture is that of a dwarfed and deformed child with diminished renal function, severe acidosis and altered calcium and phosphorus metabolism.

Four hypotheses have been advanced to explain the syndrome: (1) There is a relative or absolute inability of the kidneys to excrete waste endogenous phosphate which is then excreted through the intestinal tract. This leads to formation of insoluble calcium phosphate which prevents calcium absorption. (2) Inability of the diseased urinary tract to excrete phosphates upsets the calcium-phosphorus ratio and this leads to increased parathyroid activity which results in disturbance of calcium metabolism and resultant bone changes. Some authors consider the parathyroid hypertrophy to be primary and the renal condition secondary. (3) Harriss feels that lesions in the pituitary diencephalon area could best explain the clinical picture. Such a lesion could cause urinary tract dilatation and also dwarfism and infantilism. (4) The final theory is that chronic acidosis from long-standing renal insufficiency can cause the bone changes.

Actually most of the cases of osteonephropathy must represent combinations of these various etiological factors.

The authors present an etiological classification of osteonephropathy and describe 2 cases in detail.—*Rolfe M. Harvey.*

Henry, M. G. Anomalous fusion of the scaphoid and the greater multangular bone. *Arch. Surg.*, May, 1945, *50*, 240–241.

The author reports a case of complete bony fusion between the scaphoid and the greater multangular bone. This patient was a man of twenty-five who reported because of a recent injury. The roentgen examination showed the congenital anomaly as well as a fracture of the fused scaphoid. Generally fusion of the carpal bones is associated with synarthrosis of some of the interphalangeal joints. Fusion of carpal or tarsal bones is hereditary and the trait is transmitted according to mendelian law as a dominant factor which is not sex linked. The fact that the greater multangular and the scaphoid are the only two carpal bones which ossify at about the same time suggests that the theory of arrested development as the cause of this anomaly is plausible.—*George W. Chamberlin.*

Peck, Roy I. The treatment of skeletal metastases secondary to carcinoma of the prostate. *J.A.M.A.*, Jan. 6, 1945, *127*, 17–19.

Low back pain, with or without sciatic radiation, constitutes a fairly large part of the practice of an orthopedic surgeon. The current wave of becoming "disk conscious," either hidden or otherwise, tends to obscure the fact that there are many other lesions which are equally important in the causation of the low back syndrome. There is a small but definite group of patients over fifty with complaints of sciatica, low back pain and other bone pain which may be secondary to the metastases from carcinoma of the prostate. The metastases from this type of carcinoma are predominantly to the pelvis, sacrum and lumbar spine. These metastases may be either osteoblastic or osteoclastic, the former being by far the more common. As some of these men do not have symptoms referable to the genitourinary system, it is imperative that the rectal examination be included for any man presenting himself with low back pain. This is especially true for men over fifty. Roentgen examination of the lumbar spine and pelvis is, of course, of primary importance in making the diagnosis.

Formerly, treatment of metastases secondary to carcinoma of the prostate was mainly palliative. This included high voltage roentgen therapy, braces to decrease that portion of the pain which occurred with motion and to aid in

preventing that small percentage of cases which went on to pathologic fractures, morphine, section of nerve roots and pain pathways to the spinal cord, and intraspinal injection of absolute alcohol.

Within the last few years a new concept of prostatic carcinoma had been provided. The serum acid phosphatase level is found to be normal in that carcinoma of the prostate which is still confined within the capsule, while it is increased in local and more definitely in skeletal metastases from this neoplasm. It has been shown that the androgen increases serum acid phosphatase, while the estrogen decreases its level. Hence surgical castrations, estrogenic injections or irradiation of the testes would seem to be practical methods of diminishing androgen formation and hence would decrease the serum acid phosphatase level.

There are in the literature about 300 cases of carcinoma of the prostate treated by orchiectomy or administration of estrogen. In about 75 per cent of the cases relief of pain has followed, sometimes as soon as twenty-four to forty-eight hours. There is a gross parallelism in the drop of the serum acid phosphatase level and the clinical improvement. Orchiectomy or treatment with estrogens has not been promoted as a cure but as a physiologic method for the relief of pain, and this benefit may last one or more years. Two cases are cited in each of which carcinoma of the prostate was complicated by extensive pelvic bone metaseses. In each patient orchiectomy was followed by symptomatic relief of symptoms and by distinct healing of the metastatic bone lesions. —*S. G. Henderson.*

GREEN, WILLIAM T. Slipping of the upper femoral epiphysis; diagnostic and therapeutic considerations. *Arch. Surg.*, Jan., 1945, *50*, 19–33.

The author reports a group of 26 patients with slipping of the upper femoral epiphysis in thirty-six hips.

The cause of slipped epiphyses is unknown. It occurs most frequently in children between the ages of ten and thirteen years and at a slightly younger age in girls than in boys. Most of the children affected are obese or large in stature. The condition is frequently bilateral. In this series 10 of 26 patients had the disease on both sides.

The patient usually complained of pain and almost always had a limp. The physical examination disclosed limitation of internal rotation, flexion, and abduction of the involved hip. Limited internal rotation is usually the earliest suggestive physical finding.

The roentgen examination should include anteroposterior and lateral films. The earliest findings are rarefaction of the neck adjacent to the epiphyseal line. There is minimal displacement of the neck anteriorly on the head. This is seen best in the lateral projection. If the slipping is of some duration, irregular new bone formation may be seen filling in the angles between the head and neck of the femur. This presents a mottled appearance of increased density and rarefaction adjacent to the epiphyseal zone.

The author discusses, fairly thoroughly, the different modes of treatment which can be applied to these lesions. His best results were obtained with "traction-spica-traction" treatment and the next best results with the "nailing in situ" method without arthrotomy. He points out that the "traction-spica-traction" method requires approximately one year from the initial treatment to full activity for the patient. Those patients who have the "nailing in situ" return to full activity in a shorter time. In this group, however, there was some danger of involvement of the contralateral hip following the return to activity. It is emphasized, however, that the final evaluation of the result would require a long time follow-up, since many of these patients may develop arthritic changes later in life. —*George W. Chamberlin.*

MCPHEE, HARRY R., and FRANKLIN, C. MONTANYE. "March fracture" of the fibula in athletes. *J.A.M.A.*, June 15, 1946, *131*, 574–576.

For many years athletes at Princeton University have trained in all seasons, in all weather, and on various surfaces. Beginning in 1939, however, a series of 6 "march fractures" of the fibula were observed which exhibited considerable similarity. All occurred in athletes who had been training by running on a board surface, and in a cool atmosphere. In each patient the first symptom was nonincapacitating lameness in the involved leg, which became progressively worse. Early roentgenograms usually showed no abnormality; later, fuzziness of the periosteum at the site of the pain developed. Usually a doughy infiltration and swelling were noted in the soft tissues. A fracture line appeared in the roentgenograms about six to

eight weeks after the onset of symptoms, and its progress was typical of a fracture. With marked regularity the period of disability lasted between ten and fourteen weeks.

In 2 of the cases biopsy was requested by orthopedic surgeons before the appearance of the fracture line, because of suspected tuberculosis or a tumor. In one of the cases the leg was immobilized early, before the appearance of the fracture, but the fracture line developed later, and followed the usual course of fractures. The period of disability was thirteen weeks—five weeks before the appearance of the fracture and eight weeks afterwards.

It has been suggested that in this type of patient the fracture is present but undetected during the first stages of the disease. The authors compare the case histories of their patients to that of a patient with a typical fibular shaft fracture due to direct trauma during a game of lacrosse. The fracture was hairline in type, but weight bearing was not unusually painful. The patient was permitted to play lacrosse during the period of slightly less than four weeks needed for complete healing, with only an aluminum splint for protection.

The contrast between this type of history and the study of the 6 patients with "march fracture" of the fibula leads the authors to suggest the presence of some factor other than a simple fracture in this disease.—*E. F. Lang.*

Knutsson, Folke. Roentgenological early symptoms and healing phenomena in chronic rheumatic arthritis. *Acta radiol.*, 1943, *24*, 121–134.

Articular decalcification is described as the initial finding in rheumatoid arthritis. This is caused by the inflammatory hyperemia which occurs in this disease. An increased breadth of the joint space due to exudate may occasionally be recognized roentgenologically. As a rule, the changes are seen first in the bones of the hands and feet. The proximal joint of the little toe seems to be the favorite spot for the initial localization.

Juxta-articular periostitis is another early finding. (This observation is original with the author.) The appearance of this periostitis is typical. It consists of a short periosteal thickening extending from the joint for a short distance along the adjacent diaphysis. It is probably caused by an inflammatory irritation which has extended to the periosteum from the joint capsule. Thus this finding is seen to belong to the florid stage of the arthritis. It disappears as soon as the arthritis loses its more or less acute character. These periostites are usually located in a single toe or finger joint and they extend juxta-articularly on the phalanx or on a metacarpal or metatarsal bone. The author has found them occasionally on the radius and ulna near the wrist.

Destruction of cartilage leading to a diminution in the joint space and ulceration constitutes later roentgen findings. Again the little toe is a favorite site. Thus one often finds ulceration on the head of the fifth metatarsal bone as the only roentgenological phenomenon yielded by the examination of several joints.

The ulceration is transformed from destruction to deformity when the previously ragged, blurred and indistinct outline of the involved bones takes on an even contour due to their acquisition or a cortical covering.

Ankylosis occurs when the reduction of cartilage through the destructive nature of the arthritis has led to complete destruction and the bone surfaces come into direct contact with each other. This complete osseous fusing represents the final healing stage.—*Mary Frances Vastine.*

Jansen, Knud F. Calcareous peritendinitis; two cases with localisation to the fingers. *Acta radiol.*, 1943, *24*, 285–288.

In its commonest form as painful shoulder, calcareous peritendinitis is an old, well known clinical syndrome first described in 1870 by Duplay under the name of "periarthrite scapulohumerale." By calcareous peritendinitis we understand the deposition of calcareous material in a tendon, peritendinous tissue or joint capsule. This is most frequent in the shoulder region but it has been recognized in other sites especially in the large joints. The author has had occasion to observe 2 cases with localization in the tendons of the finger joints. This localization is extremely rare. In both of the author's cases the condition was found in the left index finger.—*Mary Frances Vastine.*

BLOOD AND LYMPH SYSTEM

Lyon, R. A., Johansmann, R. J., and Dodd, Latharine. Anomalous origin of the left coronary artery. *Am. J. Dis. Child.*, Dec., 1946, *72*, 675–690.

The cases of 2 infants with anomalous origin of the coronary arteries are reported which bring the total number of reported cases to 20.

In both patients enlargement of the heart, persistent symptoms of respiratory distress and the inversion of the T waves in the first lead or in all leads of the electrocardiogram permitted a tentative clinical diagnosis of the cardiac condition.

In the pathological examination in both cases the important abnormalities found, other than the origin of the left coronary artery from the pulmonary artery, were limited to the left ventricle, where there were endocardial fibrosis, degenerative changes of the mycoardium with replacement by fibrous tissue, infarcts in the myocardium and in 1 case persistence of embryonic sinusoids.

In the first case, roentgenographic examination showed an increase in the size of the heart. Lateral roentgenograms with iodized poppyseed oil revealed enlargement of the heart posteriorly. A film of the chest exposed three months later showed clouding of the entire lung field, left side, suggesting accumulation of fluid in the lower portion of that side of the chest. In the second case, enlargement of the heart also was shown in the teleroentgenogram. —*R. S. Bromer.*

CHRISTOPHE, LOUIS. Arteriographie de l'anevrysme carotidocaverneux. (Arteriography of a carotido-cavernous aneurysm.) *Radiol. clin.*, May, 1946, *15*, 135–142.

Dandy says that roentgenography can be dispensed with in making a diagnosis of carotido-cavernous aneurysm. But the author describes a case in which arteriorgaphy aided in such a diagnosis and believes that it would be useful in making earlier diagnoses when the communication between the vessels is very small.

His case was in a woman of fifty-seven who complained that her eyes had been red for some months. Examination showed dilatation of the conjunctival and ciliary vessels, chemosis, subconjunctival hemorrhage, pupils normal. During the examination a slight pulsation of the eyeballs was noted. There was no exopthalmus. The patient said she had not had any abnormal sound in her head. Nevertheless on the basis of the pulsation of the eyeballs a diagnosis of arteriovenous carotido-cavernous aneurysm was made.

The right common carotid was exposed to permit of cerebral arteriography. The first injection of 10 cc. thorotrast did not give a satisfactory result, nor did the second almost immediately after. With the patient still on the table a third injection was made and this definitely showed the arteriovenous aneurysm. The author believes that the failure of the first two injections to show the aneurysm must have been due to spasm of the carotid caused by irritation of the vessel walls by the thorotrast.—*Audrey G. Morgan.*

ZUPPINGER, A. Bemerkungen zur Arteriographie. (Remarks on arteriography.) *Radiol. clin.*, March, 1946, *15*, 130–133.

There are three important points in roentgenology of the blood vessels: the choice of contrast medium, the technique of making the roentgenograms and the interpretation of the results.

Thorotrast is rarely used on account of its radioactivity and its storage in the endothelial system. Vasoselectan can no longer be obtained. The contrast media used for excretion pyelography must be used. They are very painful and as a result novocain is added. The technique, which still requires improvement, is not discussed.

The chief difficulty in interpretation is the differentiation between arteriosclerosis and endarteritis obliterans. In arteriosclerosis the vessels are usually large and show generalized changes. The course, on account of the elongation caused by the loss of elasticity, is irregularly tortuous to angular; both course and contour are irregular. There are frequently dilatations even in the smaller vessels. If there is an occlusion these small vessels are at first narrow and then show a sudden dilatation.

In endangiitis obliterans the vessels are as a rule small. The changes are localized. In the acute stage the contours are irregular here too, but generally only chronic cases are seen. The course is always curved and there are no angles. If thrombi close the lumen the occlusion may be conical or transverse. There are many collaterals and they do not show angulation. Circumscribed calcification with narrowing of the lumen occurs in endangiitis and generalized calcifications in true arteriosclerosis. Arteriosclerotic and endangiitic changes occur with about equal frequency in diabetic gangrene.

Among 50 arteriograms endangiitic changes were found in 25 and arteriosclerotic changes in 9. Endangiitis causes circulatory disturbances more frequently than arteriosclerosis. If arteriorsclerosis causes circulatory disturbances it is only in old age or when there is hypertonia or diabetes.—*Audrey G. Morgan.*

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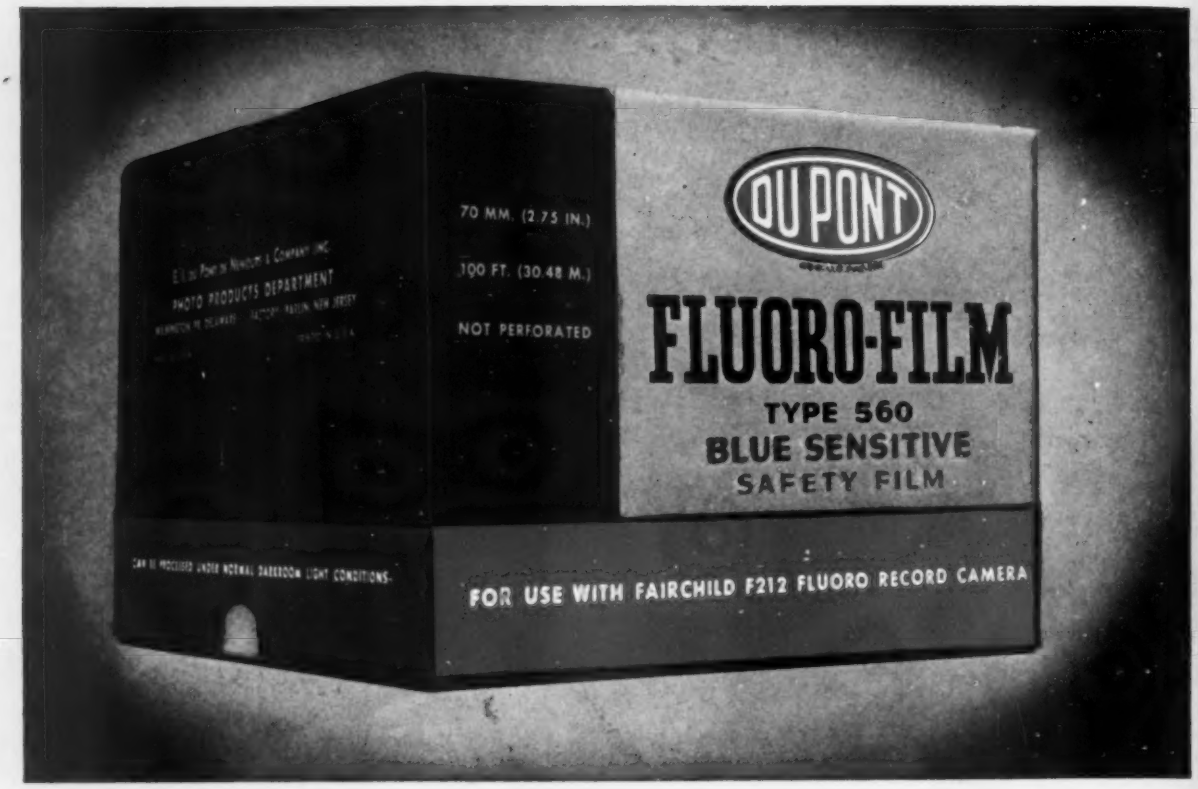

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